REMARKS

Claims 1-3, 7-17 and 25-39 were pending.

Applicants have amended claims 1, 26 and 30. Support for these amendments can be found throughout the specification as filed, for example, at Example 17.

New claims 40-44 have been added. Support for these amendments can be found throughout the specification as filed, for example, at paragraph [0142] and at Example 17.

Accordingly, no new matter is introduced by these amendments and entry of the amendments to the record is requested. Claims 1-3, 7-17, 25-44 are pending and under consideration.

35 U.S.C. § 103(a) – Obviousness

Claims 1-3 and 7-17 and 25-39 are rejected under 35 U.S.C. § 103(a) as obvious over Gewirtz et al., in view of Patel et al., Targan et al., and Sandborn et al. Gewirtz is characterized in the Office Action as reporting on the history of the development of ISIS 2302/alicaforsen, which inhibits ICAM-1. It is asserted that Gewirtz discloses that ICAM-1 plays a role in mediating inflammation, and therefore ISIS 2302 has a therapeutic potential to treat inflammatory disorders including IBD, Crohn's disease (CD) and ulcerative colitis (UC). Patel is characterized as teaching that patients with pouchitis have a significantly high level of plasma ICAM-1. Targan is characterized as teaching that patients having UC are prone to develop chronic pouchitis, which mimics the original symptoms of UC. Sandborn is characterized as teaching the development of a quantitative "Pouchitis Disease Activity Index" (PDAI) scoring system.

Based on these references, the Office concludes that it would have been obvious "to determine the effective enema dosing of alicaforsen for chronic inflammatory disease treatment as taught by Gewirtz et al., wherein the chronic inflammatory disease is chronic pouchitis..." *Office Action* at page 5. It is asserted that one of skill in the art would be motivated to do so "because Gewirtz et al. expressly taught the clinical application of enema formulation of alicaforsen (anti-ICAM-1 antisense compound ISIS 2302) would be more effective once optimal dosing is established...." *Id.* It is asserted that since ICAM-1 was known to be elevated in patients with pouchitis, and patients with UC were known to develop pouchitis and have

symptoms of UC, "the ordinary skilled artisan would have been motivated to apply the determined optimal dosing of enema formulation of alicaforsen of Gewirtz et al. for pouchitis treatment..." *Id.* Finally, it is asserted that because "the clinical utility of the instantly claimed anti-ICAM-1 ISIS 2303 in edema [*sic*] formulation for treating chronic inflammatory disease was known in the art," "an ordinary skilled artisan would have had a reasonable expectation of success in arriving at the claimed pouchitis treatment method." *Id.* at page 6. Applicants respectfully traverse.

Applicants respectfully submit that contrary to the assertions in the Office Action, Gewirtz does not establish that "the clinical utility of the instantly claimed anti-ICAM-1 ISIS 2302 in edema [*sic*] formulation for treating chronic inflammatory disease was known in the art."

With respect to the treatment of CD, Gewirtz states that the initial phase III trials of alicaforsen for CD were a failure. *Gewirtz* at Abstract. According to Gewirtz, two phase II trials of alicaforsen for CD produced mixed results – one study found the drug "considerably effective," while the other "did not show a significant effect." *Id.* at page 1402, col. 2, final paragraph. Applicants note that in at least the successful study, alicaforsen was administered by intravenous infusion, not as an enema. *See Exhibit 1*, (PubMed abstract disclosing details of cited study). Finally, Gewirtz states that a phase III trial was underway, but no results are provided. Based on the mixed results of the phase II trials, and lack of any results for the phase III trial, Gewirtz concludes that "[w]hether alicaforsen can reduce ICAM-1 expression in humans to an extent significant enough to be therapeutic in CD, at drug concentrations that do not cause unacceptable side effects, has yet to be determined." *Id.* at page 1403, col. 2, first paragraph (emphasis added). Therefore, Gewirtz does not provide a basis for concluding that the clinical utility of enema formulations of alicaforsen for treating CD "was known in the art."

As for treatment of UC, Gewirtz discloses that in December 1999, an enema formulation of alicaforsen entered phase IIa trials, "[h]owever, no further data are available." *Id.* at page 1402, col. 2, 3rd full paragraph. Clearly, as phase IIa clinical trials are the first clinical trials run to obtain preliminary data on the effectiveness of a drug, it can hardly be said that "the clinical utility" of alicaforsen in enema formulation for treating UC was "known in the art" based on this disclosure.

The assertion that there was a "reasonable expectation of success" based on Gewirtz is also not supported by the cited references. Gewirtz et al.'s statements teach that the therapeutic benefit of alicaforsen in treating CD was unknown and unpredictable:

> Whether alicaforsen can reduce ICAM-1 expression in humans to an extent significant enough to be therapeutic in CD, at drug concentrations that do not cause unacceptable side effects, has yet to be determined.
>
> While the overall available data suggest the drug has some therapeutic benefit toward this disorder, additional clinical trials are necessary before any reasonable assessment of its value can be made. ... If safe doses with efficacy levels approaching the wonderful response seen in the first double-blind placebo-controlled trial can be established, alicaforsen would be widely used in CD. Alicaforsen could be especially useful for reducing the steroid dependence of Crohn's disease patients as long-term steroid use is associated with many problems. Should effective subcutaneous or enema dosing be established, alicaforsen would be considerably more desirable. For now, antisense therapeutics such as alicaforsen remain a promising but unproven therapeutic strategy. While it seems likely that antisense drugs will eventually be clinically useful, whether it will be phosphorothioates or a later generation of antisense molecules that achieve significant clinical utility remains to be seen. *Gewirtz* at page 1403, col. 2 (emphasis added).

Gewirtz et al.'s statements indicate that the therapeutic value of alicaforsen was promising, but unproven and unknown, and that additional clinical trials were necessary "before any reasonable assessment of its value" could be made. Based on Gewirtz, one of skill in the art would conclude that additional studies were needed before there could be any reasonable expectation of success in treating Crohn's Disease using alicaforsen. If more data are needed before the value of alicaforsen for treating CD can reasonably be determined, then one of skill in the art would have to conclude that the value of alicaforsen for treating pouchitis is even less certain, and there is no reasonable expectation of success.

The Office asserts that the ordinary skilled artisan "would have been motivated to apply the determined optimal dosing of enema formulation of alicaforsen of Gewirtz et al. for pouchitis treatment" because ICAM-1 was known to be highly expressed in pouchitis, CD and UC, and because patients with UC were known to develop pouchitis and display symptoms of UC. *Office Action* at page 5.

This argument rests on the assumption that there is a "determined optimal dosing of enema formulation" which can be discovered by routine testing. However, as indicated above,

Gewirtz does not support a reasonable expectation of success in using enema formulations for treating CD or UC, let alone pouchitis.

In addition, this argument assumes that enema treatment for UC or CD will be successful in treating pouchitis, merely because they have similar symptoms, and ICAM-1 is highly expressed in all three diseases. This assumption is not supported by the evidence.

First, as Patel et al. note, "[r]aised levels of soluble forms of these intracellular cell adhesion molecules, namely sICAM-1, sE-Selectin and sVCAM-1, have been found in the plasma of a variety of disease states including chronic inflammatory liver disease [10], diabetes [11], some carcinomas [12], allograft rejection [13,14] and systemic vasculitides [15]." *Patel* at page 1037, col. 2. One of skill in the art would not expect inhibition of ICAM-1 to treat all of these various diseases – from cancer to diabetes – simply because they share elevated cell adhesion molecule levels.

Second, UC and pouchitis are distinct diseases. Some patients with UC or familial polyposis may undergo surgery to form an ileal pouch (Example 17 of the instant specification) and sometimes the pouch will develop pouchitis. That UC and pouchitis share some symptoms does not provide a basis for assuming that treatment successful for one will be successful for the other – particularly where none of the references establish that alicaforsen enemas are successful in treating either disease. For example, Kornbluth et al. disclose that the clinical practice guidelines for treating UC involve the administration of anti-inflammatory compounds, steroids and immune-suppressants. *See Kornbluth* at page 1373, col. 1, 1st full paragraph; page 1374, col. 1, first full paragraph; 1376, col. 1, second full paragraph (Exhibit 2). In contrast, pouchitis is primarily treated with antibiotics or probiotics. *See Mahadevan* at page 1640, col. 2, 2nd full paragraph (Exhibit 3). Thus, one of skill in the art would recognize that although UC and pouchitis are similar in some respects, their standard treatments are different, and there is no expectation that what is successful in treating one will be successful in treating the other.

In sum, the cited references – Gewirtz et al., Patel et al., Targan et al., and Sandborn et al. – do not provide one of skill in the art with a reasonable basis to believe that enema formulations comprising an antisense oligonucleotide having the nucleobase sequence recited in SEQ ID NO: 1 can be used to successfully treat pouchitis. None of the references demonstrate successful treatment of CD, UC or pouchitis using enemas containing ICAM-1 antisense, and Gewirtz

expressly states that more research is required before a reasonable assessment can be made of the value of ISIS-2302 for treating CD. In addition, similarities of symptoms between UC and pouchitis do not translate into similar treatments. Therefore, even *if* enemas containing ISIS 2302 were successful in treating UC, there is no expectation that it would also work for treating pouchitis.

Claims 1-3, 7-17 and 25-39 are also rejected under 35 U.S.C. § 103(a) as unpatentable over Bennett (US 6,096,722) in view of Sandborn et al. It is asserted that the '722 patent discloses a method of making enema formulations of ISIS 2302 for rectal administration, wherein pre-clinical studies show good tolerability and tissue uptake of ISIS 2302 administered by enema. It is also asserted that the '722 patent discloses "that ISIS 2302 has been evaluated up to Phase II trials for patients with Crohn's disease and ulcerative colitis, where in said ISIS 2302 has consistently demonstrated desired therapeutic efficacy. See Examples 51-55." *Office Action* at 7. Targan is cited for the disclosure that patients with UC are prone to develop pouchitis, which has similar symptoms to UC. Sandborn is cited for teaching the development of the PDAI scoring system. The Office asserts that it would have been obvious to determine the effective enema dosing of ISIS 2302 and use it to treat pouchitis, with a reasonable expectation of success through routine optimization screening experimentation. Applicants respectfully traverse.

Applicants note that the cited portion of the '722 patent, Examples 51-55, report that clinical trials on ISIS 2302 are underway, but there are no therapeutic results reported for Examples 51, 53, 54, and 55. While there are therapeutic results reported for Example 52, where ISIS 2302 shows promising results for the treatment of Crohn's disease, the compound was administered intravenously, not by enema. Thus, contrary to the assertion in the Office Action, the '722 patent does not report any therapeutic results on the use of ISIS 2302 as an enema for the treatment of any humans.

In addition, the Office is ignoring the teachings of the Gewirtz reference cited in the rejection which is discussed above. As noted previously, while Gewirtz does teach that alicaforsen has therapeutic potential, it is the authors' opinion that that potential has not yet been realized. Under the heading of "Current Opinion," the authors state that "[w]hether alicaforsen can reduce ICAM-1 expression in humans to an extent significant enough to be therapeutic in

CD, at drug concentrations that do not cause unacceptable side effects, has yet to be determined." *Gewirtz* at page 1403, col. 2, first paragraph (emphasis added). In addition, Gewirtz states that "[w]hile the overall available data suggest the drug has some therapeutic benefit toward this disorder [CD], additional clinical trials are necessary before any reasonable assessment of its value can be made." *Id.* at col. 2, second paragraph (emphasis added). Thus, when the '722 patent and Gewirtz are considered together, one of skill in the art would not have a reasonable expectation of success in treating pouchitis with an enema formulation of ISIS 2302.

Also, as noted above, the fact that UC and pouchitis share some symptoms does not provide a basis for assuming that treatment successful for one will be successful for the other – particularly where none of the references establish that alicaforsen enemas are successful in treating either disease. As discussed in detail above, one of skill in the art would recognize that although UC and pouchitis are similar in some respects, their standard treatments are different, and there is no expectation that what is successful in treating one will be successful in treating the other. Therefore, even *if* enemas containing ISIS 2302 were successful in treating UC, there is no expectation that it would also work for treating pouchitis. Thus, there is no reasonable expectation of success based on the cited references.

Claims 1-3, 7-17 and 25-39 are also rejected under 35 U.S.C. § 103(a) as unpatentable over Bennett (US 6,096,722) in view of Sachetto et al. Bennett is characterized as discussed above. It is asserted that Sachetto discloses a method of treating pouchitis using an enema comprising xanthan gum or HPMC, and that pouchitis treatment methods are interchangeable with treatment methods for UC or CD.

It is argued that it would have been obvious to use the method of administering ISIS 2302 for the treatment of UC or CD taught in the '722 patent to treat pouchitis. The Office argues that there is a reasonable likelihood of success because Sachetto teaches that UC and pouchitis treatments are interchangeable, and because the '722 patent taught that ISIS 2302 can be used to treat gastrointestinal inflammatory diseases. *See Office Action* at page 10. Applicants respectfully traverse.

As previously noted, the '722 patent does not report any therapeutic results on the use of ISIS 2302 as an enema for the treatment of any humans, and Gewirtz states that "[w]hether

alicaforsen can reduce ICAM-1 expression in humans to an extent significant enough to be therapeutic in CD, at drug concentrations that do not cause unacceptable side effects, has yet to be determined." *Gewirtz* at page 1403, col. 2, first paragraph (emphasis added). In addition, Gewirtz states that "[w]hile the overall available data suggest the drug has some therapeutic benefit toward this disorder [CD], additional clinical trials are necessary before any reasonable assessment of its value can be made." *Id.* at col. 2, second paragraph (emphasis added). Thus, when the '722 patent and Gewirtz are considered together, one of skill in the art would not have a reasonable expectation of success in treating pouchitis with an enema formulation of ISIS 2302.

This conclusion is not changed by the additional disclosure in Sachetto, which includes only a single example of treating a pouchitis with an enema formulation that does not contain antisense or any compound targeting ICAM-1. Sachetto reports that a xanthan gum enema formulation was successfully used to treat pouchitis, but does not provide any data regarding the use of the disclosed enema formulations to treat UC or CD. Thus, the actual data disclosed in Sachetto does not support the Office's assertion that Sachetto teaches that treatments for UC and pouchitis are interchangeable.

In fact, as discussed above, one of skill in the art will recognize that although UC symptoms and pouchitis symptoms are similar in some respects, these diseases are distinct from one another and their standard treatments are different. There is no expectation that what is successful in treating one will be successful in treating the other. For example, Mahadevan et al. teach that "antibiotics are the mainstay of acute and chronic pouchitis treatment." *Mahadevan* at page 1640, col. 2, 2nd full paragraph (Exhibit 3). In contrast, treatment guidelines for UC do not include antibiotics, which are apparently unsuccessful for treating UC. *See Kornbluth* at page 1373, col. 1, 1st full paragraph; page 1374, col. 1, first full paragraph; 1376, col. 1, second full paragraph (Exhibit 2). Thus, even *if* xanthan gum or HPMC enemas could treat both UC and pouchitis, there is no reason to suggest that all treatments for UC and pouchitis are interchangeable.

Finally, claims 1-3, 7-17 and 25-39 are rejected under 35 U.S.C. § 103(a) as unpatentable over Bennett (US 6,169,079) in view of Patel et al. and Sachetto et al. It is asserted that the '079 patent discloses a method of treating a human having a disease with an inflammatory component,

which is modulated by changes in human ICAM-1 comprising administering a therapeutically effective amount of an antisense oligonucleotide, including ISIS 2302, which can be administered rectally in the form of a suppository. Patel is cited for the disclosure that soluble ICAM-1 levels are elevated in pouchitis, UC and CD, especially when the disease is active. Sachetto is cited as disclosing a method of treating pouchitis using an enema comprising xanthan gum or HPMC, and that pouchitis treatment methods are interchangeable with treatment methods for UC or CD.

The Office asserts that it would have been obvious to use the method of administering ISIS 2302 for treatment of UC or CD of the '079 patent to treat pouchitis. It is asserted that there is a reasonable likelihood of success because Sachetto teaches that UC or CD disease treatments are interchangeable with pouchitis treatments, and because the '079 patent teaches that ISIS 2302-based treatment is applicable to disease with an inflammatory component modulated by ICAM-1, which is elevated in pouchitis, UC and CD as taught by Patel. Applicants respectfully traverse.

The '079 patent does not mention enemas or pouchitis anywhere. In addition, there isn't a single working or prophetic example of treating any disease with an ICAM-1 antisense formulation administered rectally, or more specifically by enema. While the '079 patent does disclose the evaluation of an ICAM-1 antisense molecule in a mouse model of inflammatory bowel disease, the antisense is administered by subcutaneous injection, not by enema. Thus, the '079 patent does not provide any basis for having a reasonable expectation that antisense to ICAM-1 can be administered by enema to treat pouchitis. In addition, as discussed above, Gewirtz states that it "has yet to be determined" whether ISIS 2302 can be used to treat inflammatory disease like CD in humans, and that "additional clinical trials are necessary before any reasonable assessment of its value can be made." *Gewirtz* at page 1403, col. 2, first and second paragraphs. Thus, when the '079 patent and Gewirtz are considered together, one of skill in the art would not have a reasonable expectation of success in treating pouchitis with an enema formulation of ISIS 2302.

This conclusion is not changed by the additional disclosure in Sachetto, which includes only a single example of treating a pouchitis with an enema formulation that does not contain antisense oligonucleotide or any compound targeting ICAM-1. Sachetto reports that a xanthan

gum enema formulation was successfully used to treat pouchitis, but does not provide any data regarding the use of the disclosed enema formulations to treat UC or CD. Thus, the actual data disclosed in Sachetto does not support the Office's assertion that Sachetto teaches that treatments for UC and pouchitis are "interchangeable."

In fact, as discussed previously, one of skill in the art will recognize that standard treatments for UC and pouchitis are different, and there is no expectation that what is successful in treating one will be successful in treating the other. For example, Mahadevan et al. teach that "antibiotics are the mainstay of acute and chronic pouchitis treatment." *Mahadevan* at page 1640, col: 2, 2nd full paragraph (Exhibit 3). In contrast, treatment guidelines for UC do not include antibiotics, which are apparently unsuccessful for treating UC. *See Kornbluth* at page 1373, col. 1, 1st full paragraph; page 1374, col. 1, first full paragraph; 1376, col. 1, second full paragraph (Exhibit 2). Thus, even *if* xanthan gum or HPMC enemas could treat both UC and pouchitis, there is no reason to suggest that all treatments for UC and pouchitis are interchangeable. The fact that soluble ICAM-1 is highly expressed in pouchitis, UC and CD as disclosed in Patel does not change this conclusion – the success of various treatments in these diseases indicates that although they have similarities, they are different diseases and treatments are not interchangeable.

Conclusion 35 U.S.C. § 103(a) rejections

Based on the above, it is clear that none of the cited references, alone or in combination, provide a reasonable basis for one of skill in the art to expect that enema formulations comprising an antisense oligonucleotide having the nucleobase sequence recited in SEQ ID NO: 1 would successfully treat pouchitis. The '722 patent does not report the successful treatment of any human disease using an enema formulation of ISIS 2302, and does not even mention pouchitis. The Gewirtz reference states that it remains to be determined if ISIS 2302 can be successfully used to treat CD, and likewise does not mention the treatment of pouchitis. Contrary to the Office's assertions, it is clear that treatments for UC or CD are not interchangeable with those for pouchitis, regardless of their shared symptoms and elevated levels of ICAM-1. Thus, as the results in Example 17 of the instant specification are unexpected and a

prima facie case of obviousness was not made by the Office, the pending claims are not obvious over the cited references.

Accordingly, for the reasons given above, Applicants request reconsideration of the rejections of the pending claims under 35 U.S.C. § 103(a) over the cited references.

No Disclaimers or Disavowals

Although the present communication may include alterations to the application or claims, or characterizations of claim scope or referenced art, Applicants are not conceding in this application that previously pending claims are not patentable over the cited references. Rather, any alterations or characterizations are being made to facilitate expeditious prosecution of this application. Applicants reserve the right to pursue at a later date any previously pending or other broader or narrower claims that capture any subject matter supported by the present disclosure, including subject matter found to be specifically disclaimed herein or by any prior prosecution. Accordingly, reviewers of this or any parent, child or related prosecution history shall not reasonably infer that Applicants have made any disclaimers or disavowals of any subject matter supported by the present application.

Patents and Applications

Applicants wish to draw the Examiner's attention to the following patents and/or applications. Applicants encourage the Examiner to review and monitor the prosecution of the following patents and/or applications, including all Office Actions, throughout the pendency of this application.

Patent / Serial Number	Title	Issued / Filed
10/793,497	COMPOSITIONS AND METHODS FOR NON-PARENTAL DELIVERY OF OLIGONUCLEOTIDES	03.04.2004
6,747,014	COMPOSITIONS AND METHODS FOR NON-PARENTAL DELIVERY OF OLIGONUCLEOTIDES	06.08.2004
09/315,298	COMPOSITIONS AND METHODS FOR NON-PARENTAL DELIVERY OF OLIGONUCLEOTIDES	05.20.1999
11/237,063	COMPOSITIONS AND METHODS FOR NON-PARENTAL DELIVERY OF OLIGONUCLEOTIDES	09.28.2005
6,169,079	OLIGONUCLEOTIDE INHIBITION OF CELL ADHESION	01.02.2001
6,300,491	OLIGONUCLEOTIDE INHIBITION OF CELL ADHESION	10.09.2001
09/659,288	OLIGONUCLEOTIDE MODULATION OF CELL ADHESION	09.12.2000
6,093,811	OLIGONUCLEOTIDE MODULATION OF CELL ADHESION	07.25.2000
6,015,894	OLIGONUCLEOTIDE MODULATION OF CELL ADHESION	01.18.2000
5,843,738	OLIGONUCLEOTIDE MODULATION OF CELL ADHESION	12.01.1998
6,096,722	ANTISENSE MODULATION OF CELL ADHESION MOLECULE EXPRESSION AND TREATMENT OF CELL ADHESION MOLECULE-ASSOCIATED DISEASES	08.01.2000
6,111,094	ENHANCED ANTISENSE MODULATION OF ICAM-1	08.29.2000
10/454,663	OLIGONUCLEOTIDE MODULATION OF CELL ADHESION	06.04.2003
6,849,612	OLIGONUCLEOTIDE MODULATION OF CELL ADHESION	02.01.2005
6,887,906	COMPOSITIONS AND METHODS FOR THE DELIVERY OF OLIGONUCLEOTIDES VIA THE ALIMENTARY CANAL	05.03.2005

08/886,829	COMPOSITIONS AND METHODS FOR THE DELIVERY OF OLIGONUCLEOTIDES VIA THE ALIMENTARY CANAL	07.01.1997
07/939,855	OLIGONUCLEOTIDE MODULATION OF CELL ADHESION	09.02.1992
5,591,623	OLIGONUCLEOTIDE MODULATION OF CELL ADHESION	01.07.1997
5,514,788	OLIGONUCLEOTIDE MODULATION OF CELL ADHESION	05.07.1996
5,883,082	COMPOSITIONS AND METHODS FOR PREVENTING AND TREATING ALLOGRAFT REJECTION	03.16.1999
07/567,286	OLIGONUCLEOTIDE MODULATION OF CELL ADHESION	08.14.1990
10/559,401	OLIGONUCLEOTIDE MODULATION OF CELL ADHESION	N/A
09/659,288	OLIGONUCLEOTIDE MODULATION OF CELL ADHESION	09.12.2000
09/082,624	COMPOSITIONS AND METHODS FOR NON-PARENTAL DELIVERY OF OLIGONUCLEOTIDES	05.21.1998

CONCLUSION

Applicants submit that the present application is in condition for allowance and respectfully requests an action to that effect. If any issues remain, the Examiner is invited to contact Applicants' counsel at the number provided below in order to resolve such issues promptly. Please charge any additional fees, including any fees for additional extension of time, or credit overpayment to Deposit Account No. 11-1410.

Respectfully submitted,

KNOBBE, MARTENS, OLSON & BEAR, LLP

Dated: 5/26/09

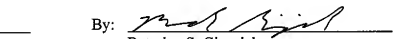
By: 

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EXHIBIT 1

1: Gastroenterology. 1998 Jun;114(6):1133-42.

Erratum in:
Gastroenterology 2001 Sep;121(3):747.

A placebo-controlled trial of ICAM-1 antisense oligonucleotide in the treatment of Crohn's disease.

Yacyshyn BR, Bowen-Yacyshyn MB, Jewell L, Tami JA, Bennett CF, Kisner DL, Shanahan WR Jr.

Division of Gastroenterology, University of Alberta, Edmonton, Canada.

BACKGROUND & AIMS: Intercellular adhesion molecule 1 (ICAM-1) plays an important role in the trafficking and activation of leukocytes and is up-regulated in inflamed mucosa in Crohn's disease. ISIS 2302 is an antisense phosphorothioate oligodeoxynucleotide that inhibits ICAM-1 expression. The aim of this study was to obtain preliminary assessment of tolerability, pharmacology, and efficacy of ISIS 2302 in Crohn's disease. METHODS: Twenty patients with active, steroid-treated Crohn's disease were randomized (3:1, ISIS 2302 to placebo) to receive over 26 days 13 intravenous infusions of ISIS 2302 (0.5, 1, or 2 mg/kg) or saline placebo in a double-blinded study. The patients were followed up for 6 months. RESULTS: At the end of treatment, 47% (7 of 15) of ISIS 2302-treated and 20% (1 of 5) of the placebo-treated patients were in remission (Crohn's Disease Activity Index [CDAI] < 150). At the end of month 6, 5 of these 7 ISIS 2302-treated remitters were still in remission, and a 6th patient had a CDAI of 156. Corticosteroid usage was significantly lower (P = 0.0001) in the ISIS 2302-treated patients. These findings were corroborated by significant increases in beta7 and alpha d bearing CD3+ peripheral blood lymphocytes and by decreases in intestinal mucosal ICAM-1 expression during the treatment period. CONCLUSIONS: ISIS 2302 seems to be a well-tolerated and promising therapy for steroid-treated Crohn's disease.

PMID: 9609749 [PubMed - indexed for MEDLINE]

EXHIBIT 2

American Journal of Gastroenterology
© 2004 by Am. Coll. of Gastroenterology
Published by Blackwell Publishing

ISSN 0002-9270
doi: 10.1111/j.1572-0241.2004.40036.x

PRACTICE GUIDELINES

Ulcerative Colitis Practice Guidelines in Adults (Update): American College of Gastroenterology, Practice Parameters Committee

Asher Kornbluth, M.D. and David B. Sachar, M.D.
The Henry D. Janowitz Division of Gastroenterology, The Department of Medicine, Mount Sinai School of Medicine; and The Practice Parameters Committee of the American College of Gastroenterology

Guidelines for clinical practice are intended to indicate preferred approaches to medical problems as established by scientifically valid research. Double-blind placebo-controlled studies are preferable, but compassionate use reports and expert review articles are utilized in a thorough review of the literature conducted through Medline with the National Library of Medicine. When only data that will not withstand objective scrutiny are available, a recommendation is identified as a consensus of experts. Guidelines are applicable to all physicians who address the subject without regard to the specialty training or interests and are intended to indicate the preferable but not necessarily the only acceptable approach to a specific problem. Guidelines are intended to be flexible and must be distinguished from standards of care, which are inflexible and rarely violated. Given the wide range of specifics in any health-care problem, the physician must always choose the course best suited to the individual patient and the variables in existence at the moment of decision.

Guidelines are developed under the auspices of the American College of Gastroenterology and its Practice Parameters Committee and approved by the Board of Trustees. Each has been extensively reviewed and revised by the Committee, other experts in the field, physicians who will use them, and specialists in the science of decision of analysis. The recommendations of each guideline are therefore considered valid at the time of their production based on the data available. New developments in medical research and practice pertinent to each guideline will be reviewed at a time established and indicated at the publication in order to assure continued validity.

INTRODUCTION

Ulcerative colitis (UC) is a chronic disease characterized by diffuse mucosal inflammation limited to the colon. It involves the rectum in about 95% of cases and may extend proximally in a symmetrical, circumferential, and uninterrupted pattern to involve parts or all of the large intestine. The hallmark clinical symptom is bloody diarrhea often with prominent symptoms of rectal urgency and tenesmus. The clinical course is marked by exacerbations and remissions, which may occur spontaneously or in response to the treatment changes or intercurrent illnesses (1, 2). UC affects approximately 250,000–500,000 individuals in the United States with an incidence of 2–7/100,000 population per year; the incidence has remained relatively constant over the last five decades (3, 4). The disease accounts for a quarter million physician visits annually, 20,000 hospitalizations, and loss of over a million work-loss days per year. The annual financial costs approach half a billion dollars annually and include hospital costs of $192 million, and drug costs of $138 million (4).

The quality of evidence on which a recommendation is based is as follows:

Grade A: Homogeneous evidence from multiple well-designed randomized (therapeutic) or cohort (descriptive) controlled trials, each involving a number of participants to be of sufficient statistical power.

Grade B: Evidence from at least one large well-designed clinical trial with or without randomization, from cohort or case-control analytic studies, or well-designed meta analysis.

Grade C: Evidence based on clinical experience, descriptive studies, or reports of expert committees.

RECOMMENDATIONS FOR DIAGNOSIS AND ASSESSMENT

In a patient presenting with persistent bloody diarrhea, rectal urgency, or tenesmus, stool examinations and sigmoidoscopy and biopsy should be performed to confirm the presence of colitis and to exclude the presence of infectious etiologies. Characteristic endoscopic and histologic findings with negative evaluation for infectious causes will suggest the diagnosis of UC.

The diagnosis of UC is suspected on clinical grounds and supported by the appropriate findings on proctosigmoidoscopy or colonoscopy, biopsy, and by negative stool examination for infectious causes. Inquiries should be made regarding factors known to exacerbate symptoms of UC, *e.g.*, recent or past smoking cessation or nonsteroidal drug use (5). Infectious etiologics of colitis can produce clinical

findings indistinguishable from idiopathic UC, so microbiologic studies for bacterial (including specific assays *for E. coli 0157:H7*) and parasitic infection, as well as serologic testing for amoeba when clinical suspicion is high, should be performed in each new patient, and should be considered in patients in remission or with mild stable symptoms who unexpectedly develop a severe exacerbation. Similarly, patients who have recently been hospitalized or treated with antibiotics should have stools examined for *Clostridium difficile*, although antibiotic-associated diarrhea may be present in the absence of *C. difficile* toxin.

Proctosigmoidoscopy or colonoscopy will reveal the mucosal changes characteristic of UC, consisting of loss of the typical vascular pattern, granularity, friability, and ulceration (6). These changes typically involve the distal rectum and proceed proximally in a symmetric, continuous, and circumferential pattern to involve all or part of the colon. However, isolated patchy cecal inflammation may be seen discontinuous from more distal inflammation in UC patients with otherwise only distal disease (7). Since none of these endoscopic findings is specific for UC, histologic findings obtained with biopsies may be helpful in the differential diagnosis. A small bowel radiograph series may also be helpful in the differential diagnosis when the diagnosis of Crohn's disease is being considered. In the patient with acute onset of bloody diarrhea, the mucosal biopsy may help in distinguishing UC from infectious colitis. In UC, more commonly than in infectious colitis, the mucosa demonstrates separation, distortion, and atrophy of crypts; acute and chronic inflammatory cells in the lamina propria, preferential homing of neutrophils to the crypt epithelium; increased number of plasma cells near the crypt bases; and basilar lymphoid aggregates (8–10). Villous mucosal architecture and Paneth cell metaplasia on rectal biopsy are other features favoring the diagnosis of UC (11). Crypt abscesses, on the other hand, are a nonspecific indication of inflammation and do not indicate a specific diagnosis (12).

Crohn's disease may be suggested by certain histologic findings such as noncaseating granulomas or microscopic focality, but their absence does not rule out the possibility of Crohn's disease. Furthermore, in acute self-limited colitis, muciphage granulomas, or intraepithelial granulomas in the presence of ruptured crypts, may be seen and are therefore not pathognomonic for Crohn's disease (11). Other histologic findings that may suggest an infectious etiology, include granulomas in tuberculosis (and even less commonly in *schistosomiasis*, *syphilis*, and *Chlamydia trachomatous*), amoebic trophozoites, pseudomembranes in *C. difficile* colitis, and viral inclusions in cytomegalovirus or herpetic colitis. In the appropriate clinical settings, sigmoidoscopy or colonoscopy and biopsy may also distinguish the various noninfectious colitides from UC. These include ischemia, radiation, collagenous and microscopic colitis, drug-induced colitis, and the solitary rectal ulcer syndrome (12).

Perinuclear antineutrophil cytoplasmic antibodies (pANCA) have been identified in 60–70% of UC patients, but are also found in up to 40% of patients with Crohn's disease. These pANCA-positive Crohn's patients typically have a clinical phenotype resembling left-sided UC, so ANCA detection alone is of little value in distinguishing between UC and Crohn's colitis (13). In a cohort of patients already known to have IBD, the combination of a positive pANCA and a negative anti-*Saccharomyces cervisiae* antibody (ASCA) had a positive predictive value of 75%, while a negative ANCA and a positive ASCA had a positive predictive value of 86% for the diagnosis of Crohn's disease (14). While, pANCA and ASCA assays at this stage of knowledge are neither a first step nor a definitive step in differential diagnosis or clinical decision-making, they may be useful in the patient in whom all other clinical features do not allow a distinction between UC and Crohn's colitis. While this distinction is not always essential, it may have direct consequences in terms of counseling, prognosis, cancer risk, and medical and surgical therapies (15).

APPROACH TO MANAGEMENT

Goals of treatment are directed at inducing and then maintaining remission of symptoms and mucosal inflammation in order to provide an improved quality of life.

Once the diagnosis of UC is confirmed, the anatomic extent is assessed endoscopically. The key question to be addressed at this point is whether the inflammation is "distal" (*i.e.*, limited to below the splenic flexure and thus within reach of topical therapy) or "extensive" (*i.e.*, extending proximal to the splenic flexure, requiring systemic medication). Therefore, a delineation of the proximal margin of inflammation, if not achieved on initial evaluation, is desirable at some point in the management of the case once the patient's condition permits.

From a practical standpoint, the anatomic extent and clinical severity of an acute attack determine the approach to therapy. Therapeutic decisions rarely are based upon histologic severity of inflammation.

Based upon clinical and endoscopic findings the disease is characterized as to its severity and extent. Severity is defined as mild, moderate, severe, or fulminant (16, 17). Patients with mild disease have less than four stools daily, with or without blood, no systemic signs of toxicity, and a normal erythrocyte sedimentation rate (ESR). Moderate disease is characterized by more than four stools daily but with minimal signs of toxicity. Severe disease is manifested by more than six bloody stools daily, and evidence of toxicity as demonstrated by fever, tachycardia, anemia, or an elevated ESR (16). However, some patients even with the most severe colitis may not demonstrate an elevated ESR. Patients with fulminant disease have features which include more than 10 bowel movement daily, continuous bleeding, toxicity, abdominal tenderness and distension, blood transfusion requirement, and colonic dilation on abdominal plain films (17).

In addition to the evaluation of the colitis extent and activity, a global assessment of the patient should include attention to extraintestinal manifestations, general health

concerns, and quality of life issues. Patients should be asked whether they have noted symptoms of ocular, oral, joint or skin or mood changes, and laboratory evaluation for anemia and liver function test abnormalities should be performed. Concerns regarding quality of life should be addressed: impairment of function at school, work or in personal relationships, social and emotional support, financial resources, and adequacy of patient education regarding their disease (5).

RECOMMENDATIONS FOR MANAGEMENT OF MILD-MODERATE DISTAL COLITIS

Patients with mild-to-moderate distal colitis may be treated with oral aminosalicylates, topical mesalamine, or topical steroids (Evidence A). Topical mesalamine agents are superior to topical steroids or oral aminosalicylates (Evidence A). The combination of oral and topical aminosalicylates are more effective than either alone (Evidence A). In patients refractory to oral aminosalicylates or topical corticosteroids, mesalamine enemas or suppositories may still be effective (Evidence A). The unusual patient who is refractory to all of the above agents in maximal doses, or who is systemically ill, may require treatment with oral prednisone in doses up to 40–60 mg per day (Evidence C).

The therapeutic plan here is largely determined by the patient's preference since either oral or topical therapy is effective; however, a metaanalysis of controlled trials indicates that topical mesalamine is superior to oral aminosalicylates in achieving clinical improvement in patients with mild-moderate distal colitis (18).

Oral therapy with the aminosalicylates, sulfasalazine, olsalazine, mesalamine, or balsalazide, is beneficial in achieving and maintaining remission (1, 19, 20, 25). Effective doses of sulfasalazine range between 4 and 6 g a day in four divided doses (21, 22); for mesalamine 2–4.8 g per day in three divided doses (23, 24), for balsalazide 6.75 g per day in three divided doses (25–27), and for olsalazine 1.5–3 g/d in divided doses (28–31), although efficacy of olsalazine in active UC is not conclusively established, perhaps in part because of a confounding dose-related diarrhea. These drugs generally act within 2–4 wk (11–20) and are effective in 40–80% of patients (18–20). Intolerance to the sulfapyridine moiety of sulfasalazine is fairly common and may result in nausea, vomiting, dyspepsia, anorexia, and headache. More severe, but less common, adverse effects include allergic reactions, pancreatitis, hepatotoxicity, drug-induced connective tissue disease, bone marrow suppression, interstitial nephritis, nephrotoxicity, hemolytic anemia, or megaloblastic anemia. Abnormal sperm counts, motility, and morphology are also related to the sulfapyridine moiety of sulfasalazine and are not seen with the mesalamine preparations (32). Approximately 80% of the patients intolerant to sulfasalazine are able to tolerate olsalazine, mesalamine, and balsalazide (19, 31, 33–35). However, several of the allergic reactions previously thought to be due to the sulfa moiety have been seen with newer aminosalicylates as well (19).

An alternative to oral aminosalicylates is topical therapy with either mesalamine suppositories or enemas, or hydrocortisone foam or enemas. Mesalamine suppositories in a dose of 500 mg twice a day are effective in the treatment of proctitis (36), and maintenance of remission (37), while mesalamine enemas in doses of 1–4 g are able to reach as proximal as the splenic flexure and are effective in inducing (38, 39) and maintaining remission in distal colitis (40–43). Topical corticosteroids, available in the United States as a 100 mg hydrocortisone enema, or as a 10% hydrocortisone foam, are effective in acute therapy of distal colitis (44–46) but have not proven effective in maintaining remission (18). Mesalamine enemas in a dose of 4 g have been more successful than corticosteroid enemas in inducing remission in two double-blind controlled studies (47–49). One-gram mesalamine enemas may prove as effective as the standard 4-g formulation for induction of remission in patients with left-sided colitis (18). Budesonide, a second generation corticosteroid that undergoes first pass hepatic metabolism has also been evaluated: the optimal budesonide enema dose, 2 mg, not yet available in the United States, seems to be at least as effective as the standard hydrocortisone preparation with fewer side effects (50, 51).

Advantages of topical therapy include a generally quicker response time and a less frequent dosing schedule than oral therapy. The choice of topical vehicle is also guided by patient preference as well as by the proximal extent of disease: suppositories reaching approximately 10 cm, hydrocortisone foam reaching approximately 15–20 cm, and enemas reaching up to the splenic flexure (52–56), although in daily clinical practice the actual extent distribution may vary.

Some patients may achieve maximum benefit from the combination of oral and topical therapy; a combination of oral mesalamine 2.4 g/d and 4 g/d mesalamine enema was more effective in achieving clinical improvement, as well as an earlier response, than either agent alone (57).

RECOMMENDATIONS FOR MAINTENANCE OF REMISSION IN DISTAL DISEASE

Mesalamine suppositories are effective in the maintenance of remission in patients with proctitis, while mesalamine enemas are effective in patients with distal colitis when dosed even as infrequently as every third night (Evidence A). Sulfasalazine, mesalamine, and balsalazide are also effective in maintaining remission; the combination of oral and topical mesalamine is more effective than the oral mesalamine alone (Evidence A). Topical corticosteroids including budesonide, on the other hand, have not proven effective for maintaining remission in distal colitis (Evidence A).

Mesalamine suppositories in doses of 500 mg daily or twice a day are effective in maintaining remission with an apparent dose-response relationship; only 10% of patients treated with 500 mg twice a day relapsed at 1 yr, compared with a relapse rate of 36% with once daily dosing (58, 59). Mesalamine enemas in doses of 2–4 g maintained remission

when dosed daily (78% effective), every other day (72% effective), or even as infrequently as every third day (65% effective) (18). Sulfasalazine in a dose of 2 g/day, olsalazine 1 g/day, Eudragit-S coated mesalamine 3.2 g/day, and balsalazide 3–6 g/day (60, 61) were all effective in maintaining remission in distal disease. The combination of oral mesalamine 1.6 g/day and mesalamine enema 4 g enema twice weekly, was more effective than the oral mesalamine alone (62). Topical corticosteroids, whether hydrocortisone or budesonide, have not proven effective for maintaining remission in distal colitis (18, 63).

RECOMMENDATIONS FOR MANAGEMENT OF MILD-MODERATE EXTENSIVE COLITIS: ACTIVE DISEASE

Patients with mild-to-moderate extensive colitis should begin therapy with oral sulfasalazine in daily doses titrated up to 4–6 g per day, or an alternate aminosalicylate in doses up to 4.8 g per day of the active 5-ASA moiety (Evidence A). Oral steroids are generally reserved for patients who are refractory to oral aminosalicylates with or without topical therapy, or for patients whose symptoms are so troubling as to demand rapid improvement (Evidence C). 6-Mercaptopurine (6-MP), or azathioprine are effective for patients who do not respond to oral prednisone but are not so acutely ill as to require intravenous therapy (Evidence C).

When the inflammation extends proximal to the reach of topical therapy (*i.e.*, mid-descending colon-splenic flexure) oral therapy is required, either solely or in combination with topical therapy (though this latter option has not been studied in randomized controlled trials). For clinically mild-to-moderate, but anatomically extensive disease, the first-line therapy traditionally has been sulfasalazine. Responses are dose-related with up to 80% of patients who receive daily doses of 4–6 g manifesting complete clinical remission or significant clinical improvement within 4 wk (21, 22) and approximately half achieving sigmoidoscopic remission (21). However, the benefits of greater efficacy with the higher dose are offset by the increase in side effects. The advantages of sulfasalazine compared with the "newer" aminosalicylates are its longer track record and considerably lower cost. If these higher doses of sulfasalazine are not well tolerated, or if there is concern regarding potential toxicity then a 5-aminosalicylate containing compound should be used at doses of at least 2 g per day, titrating up to 4.8 g per day of the active 5-aminosalicylate moiety (24).

The "newer" aminosalicylates—balsalazide (25–27), olsalazine (28–31), Eudragit-S coated mesalamine (23, 24), and ethylcellulose-coated mesalamine (64)—are all superior to placebo and equivalent to sulfasalazine in acute therapy (19). As with sulfasalazine, therapeutic benefit is dose-related, with daily doses less than 2 g being ineffective (19, 23, 24, 65). Although controlled trials have not studied the combination of oral aminosalicylates with topical treatments, patients often note a more prompt resolution of rectal symptoms when a topical therapy is added.

Controlled trials have demonstrated that transdermal nicotine patches are effective in achieving clinical improvement (66) and clinical remission (67) in patients with mild-moderate UC, with a dose-response effect between 15 and 25 mg of nicotine daily, but their success rates are generally lower than with traditional aminosalicylate therapy. Benefit was more evident in ex-smokers than in those who had never smoked (66, 68) and was better tolerated in the ex-smokers (66). The most common adverse effects were skin irritation, dizziness, and nausea. Transdermal nicotine in a daily dose of 15 mg was not effective in maintenance of remission (69) and the long-term consequences of long-term transdermal usage are uncertain. At present, it is uncertain where nicotine fits into the therapeutic algorithm.

Oral prednisone demonstrates a dose-response effect between 20 and 60 mg per day (70–73), with 60 mg per day modestly more effective than 40 mg per day but at the expense of greater side effects (72). No randomized trials have studied steroid taper schedules; many authorities (20, 73) recommend 40–60 mg per day until significant clinical improvement occurs and then a dose taper of 5–10 mg weekly until a daily dose of 20 mg is reached. At this point tapering generally proceeds at 2.5 mg/wk.

The frequency and severity of steroid toxicity are significant and may involve virtually every organ system and many metabolic activities. These include the appearance of cushingoid features, emotional and psychiatric disturbances, infections, glaucoma, cataracts, gastroduodenal mucosal injury, skin striae, impaired wound-healing, and metabolic bone disease. The latter can present insidiously with osteopenia and osteoporosis, or with the more dramatic bone fracture or unpredictable osteonecrosis. Steroid-induced metabolic disturbances include hyperglycemia, sodium and fluid retention, hypokalemia, metabolic alkalosis, hyperlipidemia, and accelerated atherogenesis (32).

The National Institute of Health have recently published their consensus statement regarding the prevention, diagnosis, and therapy of osteoporosis: any patient who is treated with a daily dose of at least 5 mg of prednisone for more than 2 months should be considered for measurement of bone mass density (74). Prospective studies on successful osteoporosis-prevention strategies in steroid-treated UC patients are lacking (75, 76). However, the American College of Gastroenterology and American Gastroenterological Association have both recently published guidelines for the diagnosis and management of osteoporosis in IBD (77, 78). DXA bone testing should be considered in IBD patients with a number of risk factors for osteoporosis such as smoking, low body mass, sedentary lifestyle, hypogonadism, family history, and nutritional deficiencies. IBD patients at greatest risk for fracture are over age 60 and all these subjects should be considered for DXA testing. Patients using corticosteroids beyond 3 months consecutively or who are recurrent users should likewise be considered for DXA testing and even prevention with bisphosphonate therapy (77). It is advisable to prescribe a bisphosphonate for IBD patients at a T

score below −2.5. For patients on long-term corticosteroids, or with other important risk factors such as previous fractures, it may be reasonable to prescribe a bisphosphonate at T scores below −1.0 (77).

Calcium supplementation 1,000–1,500 mg/day and vitamin D 800 units/day should be considered as well as estrogen replacement in the postmenopausal woman (78). Controlled trials have demonstrated efficacy for alendronate (79), risedronate (80), and etidronate in the prevention of corticosteroid-induced osteoporosis (81) in non-IBD populations. Modifiable risk factors, such as cigarette smoking, alcohol use, and a sedentary lifestyle should be addressed. For the patient with significant bone loss, referral to a specialist should be considered.

Controlled (82, 83) and uncontrolled trials (84, 85) of azathioprine in doses up to 1.5–2.5 mg per kg per day have demonstrated its effectiveness in patients who do not respond to, or cannot be weaned from steroids. Uncontrolled series have also demonstrated its value in achieving remission in patients refractory to high doses of oral steroids (84, 86). In this capacity, its use in acute induction of remission is somewhat limited by its slow onset of action; up to 3–6 months of treatment may be necessary to appreciate an optimal effect (87).

Azathioprine and 6-MP toxicities include bone marrow suppression, particularly leukopenia, which is usually dose-dependent. Serious infections are infrequent and are usually, but not always, related to leukopenia and often occur with concomitant steroid use. Liver abnormalities occur in approximately 2% of patients and usually represent a reversible drug-induced hepatitis. Allergic reactions occur in approximately 2–5% of patients and usually present as some combination of fever, rash, myalgias, or arthralgias. Pancreatitis occurs as a hypersensitivity reaction in approximately 2% of patients (88). Long-term use has not been associated with increased neoplasia risk (89, 90).

Some (91, 92) but not all (93, 94) recent retrospective data have suggested that measurement of azathioprine and 6-MP metabolites may be useful in dose adjustments since serum 6-thioguanine nucleotide (6-TGN) levels of greater than 235 pmol/8 × 10^8erythrocytes may be associated with a greater response rate than patients with lower 6-TGN levels. Hepatotoxicity, on the other hand, may correlate with the elevated levels of 6-methylmercaptopurine (6-MMP). A retrospective study (95) found that a subset of patients with 6TGN levels of less than 235 pmol/8 × 10^8erythrocytes may remain refractory to dose escalations of 6-MP/AZA since they may preferentially metabolize 6-MP/AZA to 6-MMP and maintain suboptimal 6TGN levels (95). Given the conflicting data, the retrospective nature of these studies, and the limited positive and negative predictive values for these particular uses, the utility of these tests need prospective controlled evaluation before their routine use can be recommended. However, these metabolite markers can be of value in assessing whether a patient is noncompliant with their immunomodulator therapy. Leukopenia was observed in only 8% of responders, indicating that it is not a necessary condition for effective dosing (91).

6-MP and its prodrug azathioprine are both metabolized by thiopurine methyltransferase (TPMT), an enzyme that exhibits variation as a result of a genetic polymorphism of its alleles and this enzyme can now be measured by commercial laboratories. Approximately 0.3% of the general population have low to absent enzyme activity, 11% have intermediate, and 89% have normal to high levels of activity (96). However, only about a quarter of cases of leukopenia in practice are associated with one of these genetic polymorphisms (97). Therefore, prospective studies of dose-optimization based on measurements of TPMT, 6-TG, or 6-MP levels to monitor clinical response are still needed before the routine use of these assays can be recommended as providing much incremental benefit to the traditional routine of monitoring the CBC, liver associated laboratory chemistry abnormalities, and clinical response.

As described below, azathioprine has been found effective in maintaining remission in a controlled drug withdrawal study (98), while retrospective studies have demonstrated the value of 6-MP in maintaining long-term remission (99, 100) and is generally well tolerated during the long-term use (88–90, 99).

Methotrexate has not been proven to be effective in UC when administered in a weekly dose of 12.5 mg/day (101); higher doses, or administration by a parenteral route has not been studied in controlled trials.

RECOMMENDATIONS FOR MILD-MODERATE EXTENSIVE COLITIS: MAINTENANCE OF REMISSION

A maintenance regimen is usually required when the acute attack is controlled, especially in patients with extensive, or relapsing disease. Sulfasalazine, olsalazine, mesalamine, and balsalazide are all effective in reducing relapses (Evidence A). As a rule, patients should not be treated chronically with steroids. Azathioprine or 6-MP may be useful as steroid-sparing agents for steroid-dependent patients and for maintenance of remission not adequately sustained by aminosalicylates, and occasionally for patients who are steroid-refractory but not acutely ill (Evidence C).

Sulfasalazine reduces relapse rates in UC in a dose-related fashion, with benefits demonstrated at 2–4 g per day (102–104). Although the 4 g per day regimen is the most effective in preventing relapse, up to one quarter of patients cannot tolerate the side effects at this dose, thus limiting its overall utility (104). The newer aminosalicylate preparations—including olsalazine (105, 106), mesalamine (107–115), and balsalazide (116)—have relapse-prevention properties virtually the same as, but not greater than, those of equivalent doses of sulfasalazine (19, 117). Because of the well-documented efficacy of sulfasalazine in relapse-prevention, most (107, 108, 110, 111, 114, 119–124) but not all (115, 118), 5-ASA relapse-prevention trials have used sulfasalazine as the control. As with sulfasalazine, most (115, 124–127), if not all

(128, 129), comparison studies of mesalamine have demonstrated increased efficacy with higher doses up to 4 g per day of 5-ASA. However, unlike sulfasalazine, use of larger doses of 5-ASA in the newer preparations are generally well tolerated, lending these analogues an advantage over sulfasalazine for relapse-prevention. On the other hand, the cost of sulfasalazine, especially when considered for long-term use, is considerably lower. Although the maximum length of remission-maintenance benefit has not been established, most experts recommend permanent maintenance; however, the patient with a mild first episode, or with very infrequent mild relapses that are easily controlled, may opt for being followed without long-term medical maintenance therapy.

The immunomodulators azathioprine and 6-MP have been studied for relapse-prevention. (As with induction of remission in UC, there have been no studies comparing 6-MP with azathioprine.) In patients whose remission was achieved with azathioprine, continuation of active drug reduced the 12-month relapse rate to 36%, compared to 59% on placebo (98). Similarly, uncontrolled retrospective data from 105 patients treated with continued long-term 6-MP (99), and 351 patients treated with long-term azathioprine (100) appear to confirm the efficacy of these agents continued long-term in maintaining remissions of UC. The risk-benefit ratio of indefinite azathioprine or 6-MP use, especially when compared to colectomy, for the maintenance of remission, is not known, although a recent retrospective series of 621 IBD patients treated during a 30-yr interval indicated that azathioprine is generally well tolerated (89) and is not associated with an increased cancer risk (90) or mortality (100).

RECOMMENDATIONS FOR MANAGEMENT OF SEVERE COLITIS

The patient with severe colitis refractory to maximal oral treatment with prednisone, oral aminosalicylate drugs, and topical medications, or the patient who presents with toxicity, should be hospitalized for a course of intravenous steroids (Evidence C). Failure to demonstrate significant improvement within 7–10 days is an indication for either colectomy (Evidence C) or treatment with intravenous cyclosporine (Evidence A) in the patient with severe colitis. Long-term remission, in these patients is significantly enhanced with the addition of long-term maintenance 6-MP (Evidence C).

The patient who continues to have severe symptoms despite optimal doses of oral steroids (40–60 mg of prednisone daily), oral aminosalicylates (4–6 g of sulfasalazine, 4.8 g of mesalamine, or 6.75 g of balsalazide), and topical medications as tolerated, should be hospitalized for further treatment (130–137). Superimposed infection with enteric pathogens and *C. difficile* should be excluded. The mainstay of therapy at this point is an intravenous steroid in a daily dose equivalent to 300 mg of hydrocortisone or 60 mg of methylprednisolone if the patient has received steroids in the prior month, or perhaps intravenous ACTH if the patient has not recently received steroids, as has been suggested by some, but not all series (134–136). There is no benefit to treatment with a much higher daily dose of steroids and it exposes the patient to a higher potential rate of side effects (137). The clinical impression that continuous infusion is preferable to bolus therapy has not been subjected to a controlled trial. Controlled trials of antibiotics, however, have demonstrated no therapeutic benefit from the use of oral vancomycin (138), intravenous metronidazole (133), or ciprofloxacin (139), when added to intravenous steroids. However, protocols outlining treatment regimens for severe colitis generally include broad-spectrum antibiotics for patients with signs of toxicity, or with worsening symptoms despite maximal medical therapy (130–132).

There is a prevalent tendency to place patients with severe colitis almost routinely on total parenteral nutrition (TPN). Controlled studies on this subject, however, show no benefit from this maneuver (140, 141) as a primary therapy for UC, which may even be detrimental by depriving the colonic enterocytes of the short-chain fatty acids vital to their metabolism and repair (142). However, TPN may be useful as a nutritional adjunct in patients with significant nutritional depletion (143).

There are no studies to demonstrate that an oral aminosalicylate is of clinical benefit in this setting either, so it is generally withheld if the patient is NPO, but it may be continued if the patient is eating and has been tolerating this drug. Likewise, no controlled studies have confirmed any incremental benefit of topical medications in this setting, but they are still often prescribed if they can be retained and tolerated. Since the failure rate of medical therapy in patients hospitalized for severe colitis is approximately 40% (144), these patients should be followed closely in conjunction with a surgeon experienced in the management of patients with inflammatory bowel disease.

Infrequently, cytomegalovirus superinfection may occur in the patient with severe colitis and this possibility should be considered in the patient who is not responding to maximal immunosuppressive therapy. CMV superinfection can be diagnosed with sigmoidoscopic biopsy and viral culture and treatment with gancyclovir may lead to clinical improvement (145, 146).

In patients with either toxic signs (fever, leukocytosis, or worsening symptoms) or megacolon, medications with anticholinergic or narcotic properties should be avoided for fear of worsening colonic atony or dilatation. Patients with severe colitis who do not improve significantly after 7–10 days of maximal medical therapy are unlikely to benefit from prolongation of this medical treatment (132, 134) and should either be referred for surgery (see below) or offered treatment with intravenous cyclosporine. In one placebo-controlled double-blind trial, 82% of patients with steroid-refractory severe colitis, treated with intravenous cyclosporine in a dose of 4 mg per kg per day improved and were able to avoid colectomy in the acute stage (147); another series demonstrated similar efficacy with an intravenous cyclosporine dose of 2 $mg/kgday^{-1}$ (148). Patients with fulminant colitis are treated similarly but decisions regarding surgery *versus* cyclosporine should

be made within a few days of initiating intravenous steroid therapy.

No randomized controlled trials have been performed studying the addition of azathioprine or 6-MP to cyclosporine. Retrospective series with long-term follow-up of up to 5.5 yr (149) indicate a significantly higher long-term success rate when azathioprine or 6-MP were added during the oral cyclosporine phase (148–152), although the ideal dose or time to add 6-MP or azathioprine has not been studied. In the largest reported series the long-term success rate, defined as the avoidance of subsequent courses of intravenous steroids or colectomy, was 76% when 6-MP was added, *versus* 23% in patients in whom 6-MP was not added, during follow-up of 3.6 yr (150).

Significant toxicity may occur with cyclosporine use in UC. Severe adverse events include nephrotoxicity, infection, and seizures (particularly in patients with associated hypocholesterolemia or hypomagnesemia). More common, but less severe side effects include paresthesias, hypertension, hypertrichosis, headache, abnormal liver function tests, hyperkalemia, and gingival hyperplasia (153). Based on data from a small series, it has been suggested that cyclosporine does not increase the rate of postoperative complications in patients undergoing proctocolectomy (154) while the preoperative use of corticosteroids in patients with inflammatory bowel disease does substantially increase the risk of postoperative infections in patients undergoing elective bowel surgery (155).

Patients with fulminant colitis or toxic megacolon should be treated as above; in addition they should be kept NPO, have a small bowel decompression tube if a small bowel ileus is present, and instructed to rotate frequently into the prone or knee-elbow (156) position to aid in evacuation of the bowel gas. Broad-spectrum antibiotics are usually used empirically in these patients. The duration of medical treatment of megacolon is controversial; some experts advocate surgery within 72 h if no significant improvement is noted (157) while others take a more watchful stance if no toxic symptoms are present (156). All agree, however, that any clinical, laboratory, or radiologic deterioration on medical therapy mandates immediate colectomy.

RECOMMENDATION FOR SURGERY

Absolute indications for surgery are exsanguinating hemorrhage, perforation, and documented or strongly suspected carcinoma (Evidence C). Other indications for surgery are severe colitis with or without toxic megacolon unresponsive to conventional maximal medical therapy, and the patient with less severe, but medically intractable symptoms or intolerable medication side effects (Evidence C).

There are no prospective randomized trials comparing medical treatment to surgery for any indication in UC, but three situations are absolute indications for surgery since continued medical therapy is doomed to failure and potentially fatal: exsanguinating hemorrhage, frank perforation, and documented or strongly suspected carcinoma, *i.e.*, high-grade dysplasia or possibly low-grade dysplasia in flat mucosa (see in section "Recommendations for Cancer Surveillance").

Massive hemorrhage in UC is due to diffuse mucosal ulceration. If the hemorrhage is exsanguinating or even persisting despite maximal medical therapy (see above), it is an indication for emergency surgery. If the patient's condition permits, total proctocolectomy may be the most reliable procedure since a small group (approximately 12%) of patients may have continued hemorrhage from the retained rectal segment if only a subtotal colectomy is performed (158, 159). On the other hand, subtotal colectomy with the preservation of the rectum for a future restorative procedure is an acceptable choice, so long as the small risks of further hemorrhage are appreciated and appropriately monitored.

Perforation, fortunately occurring in only 2–3% of hospitalized UC patients at tertiary referral centers (160), is the most dreaded and most lethal complication of toxic colonic dilation. In a univariate analysis, perforation had a more adverse impact on survival than any other single clinical variable (160). Moreover, it is essential to recognize that perforation can occur without being preceded by megacolon. The surgical procedure of choice in this setting is a subtotal colectomy with rectosigmoid mucous fistula or Hartmann's closure (160).

Other indications for surgery include the patient with severe colitis or toxic megacolon unresponsive to maximal intravenous medical therapy (see above). The patient with less severe but medically intractable symptoms, resulting in physical debility, psychosocial dysfunction, or intolerable steroid side effects, may also be best served by colectomy. However, uncontrolled series suggest that approximately 2/3 of these patients may achieve remission with the use of the immunosuppressive drugs azathioprine or 6-MP (85, 99).

Only rarely is surgery necessary to control the extraintestinal manifestations of UC (161). Likewise, patients with severe, progressive pyoderma gangrenosum, in whom the pyoderma activity parallels the activity of the colitis (162), or with hemolytic anemia refractory to steroids and splenectomy, may benefit from colectomy (163, 164). By contrast, the course of primary sclerosing cholangitis (PSC) is independent of the activity of the colitis and is not affected by colectomy (165).

Whatever the indication for surgery, patients should be informed of the different operations available (*i.e.*, total proctocolectomy with permanent ileostomy *vs* the ileoanal anastamosis procedure) and be aware of the risks and benefits of these operations within different clinical settings.

RECOMMENDATIONS FOR THE MANAGEMENT OF POUCHITIS

Patients who develop the typical symptoms of pouchitis after the ileoanal pouch anastomosis (IPAA) should be treated with a short course of antibiotics (Evidence A). Although controlled data are scarce, metronidazole in a dose of 250 mg

thrice a day or ciprofloxacin 500 mg twice a day are most commonly used (Evidence C).

Patients who undergo the IPAA procedure may develop an idiopathic inflammation termed "pouchitis," which typically presents with variable symptoms of increased stool frequency, rectal bleeding, abdominal cramping, rectal urgency, tenesmus, incontinence, fevers, and the appearance of extraintestinal manifestations (166). The diagnosis can be made clinically and is associated with characteristic endoscopic and histologic features (167); symptoms do not always correlate with endoscopic and histologic findings (168). Demonstrating the diagnosis with pouchoscopy as opposed to empiric treatment with metronidazole may be a cost-effective strategy (169). Pouchitis occurs in up to 50% of patients after a mean follow-up of 40 months (170) and occurs more frequently in patients with PSC or other preoperative extraintestinal manifestations (171). Only rarely does refractory or recurrent pouchitis occur because of the missed diagnosis of Crohn's disease (172), and pouch excision is required in fewer than 5% of patients in most series. Some patients with episodes of increased stool frequency and cramping, but with normal endoscopic and histologic findings in the pouch, may be experiencing "irritable pouch" symptoms and may respond to anticholinergics, antidepressants, and antidiarrheals. Other patients may have inflammation limited to a short cuff of retained rectal mucosa ("cuffitis") and may respond to topical hydrocortisone or mesalamine (173).

Controlled drug trials for the treatment of pouchitis are very limited (174, 175). Metronidazole 400 mg thrice a day was effective in the treatment of chronic active pouchitis (177), while other controlled trials demonstrated at least similar efficacy to metronidazole with ciprofloxacin 500 mg twice a day (175), or with budesonide enema 2 g daily (176). Numerous uncontrolled trials demonstrate similar efficacy with metronidazole as well as with other antibiotics (170, 178), as well as oral mesalamine, and topical mesalamine and steroids. An oral probiotic formulation VSL-3 (containing lactobacilli, bifidobacteria, and *Streptococcus salivarius*), was effective in the prevention of pouchitis for up to 1 yr following surgery) (179), and in the prevention of pouchitis relapse (180).

RECOMMENDATIONS FOR CANCER SURVEILLANCE

After 8–10 yr of colitis, annual or biannual surveillance colonoscopy with multiple biopsies at regular intervals should be performed (Evidence B). The finding of high-grade dysplasia in flat mucosa, confirmed by expert pathologists' review, is an indication for colectomy, while the finding of low-grade dysplasia in flat mucosa may also be an indication for colectomy to prevent progression to a higher grade of neoplasia (Evidence B).

Patients with UC are at increased risk for colorectal cancer; the degree of risk is related to the duration of disease and anatomic extent of colitis (181, 182). After 10 yr of universal disease, the cancer risk is in the range of 0.5–1% per year (181–185). Even patients with left-sided colitis reach similar levels of cumulative cancer-risk after 3–4 decades of disease (182, 186, 187); patients with proctitis or proctosigmoiditis are not at increased cancer risk. Although some data suggest a later onset of cancer risk in left-sided than in more extensive colitis (181), this evidence is not sufficiently strong to justify different guidelines for surveillance in the two groups. Determination of anatomic extent in assessing cancer risk has historically been based on macroscopic rather than histologic inflammation. On the other hand, both macroscopic and microscopic healing may occur, but once extensive colitis is documented, the cancer risk should be assumed to correlate with the greatest previously determined extent. Some (188, 189), but not all (190, 191) groups have found that patients with UC and PSC have an increased risk of colorectal cancer. Whether this observation reflects a true biologic phenomenon or a statistical artifact of longer than appreciated colitis duration, it is prudent to start colonoscopic surveillance as soon as the coexisting diagnoses of UC and PSC are established (190, 191). In a recent, prospective randomized, placebo-controlled trial, ursodeoxycholic acid in daily divided doses of 13–15 mg/kg, significantly reduced the risk for developing colorectal neoplasia in patients with UC and PSC (192).

UC patients with a family history of colorectal cancer have a five-fold risk of cancer compared with the matched controls (193). On the other hand, population-based data suggest that there is a reduced relative cancer risk in patients who are taking at least 2 g/day of an aminosalicylate (194, 195), or who visit a physician at least twice a year (194). Similarly, a chemoprotective effect has been suggested in some (196, 197), but not all series (198), for sulfasalazine; an effect that may be confounded in part by its effect on folate metabolism (198).

Compared with noncolitis associated colorectal cancer, colitis-associated cancers are more often multiple, broadly infiltrating, anaplastic, and uniformly distributed throughout the colon, and seem to arise from flat mucosa instead of following the usual adenoma-cancer sequence (182, 187, 199). Furthermore, colitis-associated colorectal cancer often occurs in a much younger patient population than does colorectal cancer in the general population (182, 184).

Simply stated, the goals of any cancer surveillance program in UC are to prevent cancer and to save lives. There are no randomized studies comparing different surveillance protocols or, for that matter, even surveillance *versus* no surveillance. Nonetheless, at present, the best practical recommendation for patients who are surgical candidates, based upon review of dysplasia surveillance series calls for annual or biannual colonoscopy, avoiding periods of clinical relapse, with multiple biopsies at 10-cm intervals (200–202). Examination every second year would reduce the cost but at the expense of reducing likelihood of early cancer detection (200), especially in patients with longer disease duration since hazard rates increase with time (203, 204). Whatever schedule might be theoretically most advisable, being both frankly informative and programmatically flexible with patients is important to compliance. The cost of such a surveillance program for each

successful detection of precancer or cancer compares favorably with the cost of population-wide screening by flexible sigmoidoscopy for all subjects at average risk for colorectal cancer (201). Patients with longstanding UC may also be offered the option of a prophylactic total proctocolectomy, but patients in remission rarely opt for this approach.

The standardization of "high-grade" and "low-grade" dysplasia published by the Inflammatory Bowel Disease—Dysplasia Morphology Group (IBD-DMG) has been widely adopted and has served to make the diagnosis of dysplasia more stringent (205). When colon cancer is identified the need for surgery is obvious; similarly, the colonoscopic biopsy diagnosis of high- or low-grade dysplasia in flat mucosa is often indicative of a concurrent or future cancer and is an absolute indication for colectomy for patients with high-grade dysplasia (206, 207), and should prompt consideration of colectomy in patients with low-grade dysplasia as well.

The finding of low-grade dysplasia in a mass lesion (208) that does not resemble a typical sporadic adenoma (see below), or a stricture that is symptomatic, or is not passable during colonoscopy (209, 210) especially in longstanding disease, are likewise often seen in conjunction with colon cancer and colectomy is advisable. The findings of low-grade dysplasia in flat mucosa may also be an indication for colectomy since an analysis of 10 prospective series of dysplasia surveillance in 1,225 patients found cancer at colectomy immediately after colonoscopic biopsy evidence of low-grade dysplasia in 19% of patients (211), while the 5-yr predictive value of low-grade dysplasia for either cancer or high-grade dysplasia is as high as 54% (212–214).

How to manage the patient with longstanding UC, who is found to have a polypoid mass within a colitic area, that resembles a typical sporadic adenoma, *i.e.*, an adenoma-like mass (215)? Two recent series reported 72 such patients who had a polypoid mass resected in its entirety by colonoscopic polypectomy (216, 217) and who had no dysplasia in the adjacent flat mucosa. Although longer-term data are required, during a mean follow-up of 3.9 yr no dysplasia in flat mucosa or carcinoma was found, suggesting that vigilant follow-up surveillance colonoscopy may suffice for these patients. Polyps with a plaque or carpet-like morphology were excluded from these studies and should continue to be considered dysplasia associated with a lesion or mass (DALM) and requires surgery.

Guidelines for the patient found to have low-grade or high-grade dysplasia are discussed above. It is essential to obtain corroborating pathologic review to confirm the unequivocal distinction between definite neoplastic dysplasia and regenerative atypia due to inflammation and repair. However, attempts to repeatedly demonstrate dysplasia on subsequent examinations before recommending colectomy should not be undertaken without the awareness by both patient and physician of the high risk of concomitant or subsequent advanced neoplasia. On the other hand, the patient whose biopsies are interpreted as "indefinite" for dysplasia should have the slides reviewed by an expert gastrointestinal pathologist and should undergo repeat surveillance colonoscopy at a briefer interval (205), since these patients may have an elevated risk of subsequent progression to definite dysplasia (218).

ACKNOWLEDGMENT

We gratefully acknowledge the assistance of Michele Kissous-Hunt in the preparation of this manuscript.

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Received April 5, 2004; accepted April 6, 2004.

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EXHIBIT 3

Diagnosis and Management of Pouchitis

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The disease pouchitis was first reported by Kock[1] in 1977 as an inflammatory condition of the continent ileal reservoir (Kock pouch) in patients who had undergone proctocolectomy. The Kock pouch was later replaced by the ileal pouch anal anastomosis (IPAA, also known as the ileoanal pouch) which was independently described by Parks and Utsunomiya[2,3] in 1980. The ileoanal pouch is now the surgical option of choice in patients with familial adenomatous polyposis (FAP) and ulcerative colitis (UC) with either dysplasia or disease refractory to medical therapy. Pouchitis is the most common long-term complication of IPAA in UC.[4] This review discusses the diagnostic criteria, cause, and management of acute and chronic pouchitis.

Definition

The variation in the reported frequency of pouchitis at different centers and at the same center at different points in time is a reflection of the lack of uniform classification and diagnostic criteria. The definition of pouchitis has evolved to encompass clinical, endoscopic, and histologic criteria. A sensitive but nonspecific designation developed by the Mayo Clinic in 1987 defined pouchitis as a clinical syndrome of watery, frequent, at times bloody stool accompanied by urgency, incontinence, abdominal cramps, malaise, and fever. The symptoms must be present for at least 2 days and should be relieved within 48 hours by metronidazole therapy.[4] A more specific diagnostic criteria proposed by the St. Marks Hospital defined pouchitis as a triad of diarrhea (≥6 stools/day), endoscopic findings (≥ 4 findings of edema, granularity, friability, loss of vascular pattern, mucosal hemorrhage, or ulceration), and a minimum grade of 4 in a 6-point histopathologic index (polymorphonuclear leukocyte infiltration and percent ulceration per low-power field).[5]

The Pouchitis Disease Activity Index (PDAI) was developed in 1994, incorporating the Mayo Clinic definition and the St. Marks pouchitis triad and histopathologic index.[6] The PDAI attempted to provide a standardized definition of pouchitis based on clinical, endoscopic, and histologic markers (Table 1), with pouchitis defined as a score greater than or equal to 7 points. The specificity and sensitivity of diagnosis was increased by defining the disease as a continuum from mild to severe pouchitis with symptoms individualized to the norms of each patient. The operational use of the PDAI has evolved such that active pouchitis is defined as a PDAI score greater than or equal to 7 points in a patient with a definite diagnosis of pouchitis, whereas a PDAI score greater than or equal to 7 points in a patient with a history of a definite diagnosis of pouchitis indicates that the pouchitis is in remission.

In 2001, Heuschen described the Heidelberg Pouchitis Activity Score (PAS),[7] which again attempted to provide a common definition of pouchitis (Table 2). The PAS and PDAI are very similar with the major exception of the inclusion within the former of chronic inflammation as a variable in the histopathology category, the exclusion of fever among the clinical symptoms, and minor variations in the endoscopic score. Heuschen then applied both the PAS and PDAI to 41 patients over 103 outpatient visits and compared them with the gold standard of a physician and surgeon's independent diagnosis of pouchitis.[8] The clinicians diagnosed pouchitis in 24.3% of patients, the PAS in 35.9%, and the PDAI in 17.5%. When compared to the clinician, the PAS had a sensitivity and specificity of 84% and 79.5%, respectively, while the PDAI had a sensitivity and specificity of 60% and 96.2%, respectively. In patients with and without pouchitis, there was no significant difference in the clinical symptoms score in the PAS or the PDAI, but there was a difference in the total endoscopic score and the total histologic score. In addition, although the endoscopic and histologic examinations correlated in both the PAS and the PDAI, there was no correlation

Abbreviations used in this paper: EIM, extraintestinal manifestations; FAP, familial adenomatous polyposis; IL, interleukin; IPAA, ileal pouch anal anastomosis; pANCA, serum antineutrophil cytoplasmic antibody-perinuclear staining pattern; PAS, Pouchitis Activity Score; PDAI, Pouchitis Disease Activity Index; PSC, primary sclerosing cholangitis; QOL, quality of life; SCFA, small chain fatty acids.

0016-5085/03/$30.00
doi:10.1016/S0016-5085(03)00325-1

between clinical and endoscopic or clinical and histologic findings in either scoring system.

Overall, the PAS seems to overestimate pouchitis by 11% and the PDAI seems to underestimate pouchitis by 18% when compared with the gold standard of the clinician's assessment. Both the PDAI and the Heidelberg PAS need to be revalidated to determine the scores required to define symptomatic remission and global remission, and to determine the minimum clinically significant difference in the scores needed to define symptomatic improvement and global improvement.

Once a diagnosis of pouchitis is made, it can be further classified.[9] The activity of pouchitis is stratified as remission (no active pouchitis), mild to moderately active (increased stool frequency, urgency, infrequent incontinence), or severely active (hospitalization for dehydration, frequent incontinence). The duration of pouchitis is defined as acute (≤ 4 weeks) or chronic (> 4 weeks) and the pattern of pouchitis is classified as infrequent (1 or 2 acute episodes), relapsing (≥ 3 acute episodes), or continuous. Finally, the response to medical therapy is labeled as treatment-responsive or treatment-refractory with the medications for either case specified.

Table 1. The Pouchitis Disease Activity Index

Clinical criteria	Score
Stool frequency	
Usual postoperative stool frequency	0
1–2 stools/day > postoperative usual	1
3 or more stools/day > postoperative usual	2
Rectal bleeding	
None or rare	0
Present daily	1
Fecal urgency/abdominal cramps	
None	0
Occasional	1
Usual	2
Fever (temperature > 100°F Farenheit)	
Absent	0
Present	1
Endoscopic criteria	
Edema	1
Granularity	1
Friability	1
Loss of vascular pattern	1
Mucus exudates	1
Ulceration	1
Acute histologic criteria	
Polymorph infiltration	
Mild	1
Moderate + crypt abscess	2
Severe + crypt abscess	3
Ulceration per low-power field (average)	
<25%	1
≥25% ≤ 50%	2
>50%	3

Pouchitis is defined as a total PDAI score ≥ 7 points.
Adapted with permission from: Sandborn WJ, Tremaine WJ, Batts KP, Pemberton JH, Phillips SF. Pouchitis following ileal pouch-anal anastomosis: a pouchitis disease activity index. Mayo Clin Proc 1994;69: 409–415.

Table 2. The Heidelberg Pouchitis Activity Score: Maximum 36 Points

Clinic	Score		Score
1. Stool frequency/ 24 hours		2. Fecal urgency	
< 8	0	absent	0
8–10	2	present	3
11–13	4		
>13	6		
3. Rectal bleeding			
absent	0		
present	3		
			Max. 12
Endoscopy	**Score**		**Score**
1. Edema		2. Granularity	
absent	0	absent	0
present	1	present	1
3. Friability		4. Erythema	
absent	0	absent	0
mild	1	mild	2
severe	2	severe	3
5. Flattening of mucosal surface		6. Ulcerations/erosions	
absent	0	absent	0
present	2	mild	2
		severe	3
			Max. 12
Histology	**Score**		**Score**
1. Acute histologic inflammation		2. Chronic histologic inflammation	
Polymorphonuclear leukocyte infiltration		Mononuclear leukocyte infiltration	
absent	0	absent	0
discrete and patchy (largely confined to surface epithelium)	1	mild and patchy	1
moderate with (±) crypt abscesses or cryptitis	2	moderate	2
extensive with (±) crypt abscesses or cryptitis	3	extensive	3
Ulcerations/erosions		Villous atrophy	
absent	0	absent	0
mild and superficial	1	minimal	1
moderate	2	partial	2
extensive	3	subtotal/total	3
			Max. 12

Reprinted with permission from Heuschen et al. Dis Colon Rectum 2001;44:487–499.

Diagnostic Tests

The key point of both the PDAI and the PAS is that endoscopic and histopathologic evaluation is required to make the diagnosis of pouchitis. This finding was corroborated by Shen[10] in a study applying the PDAI to the evaluation of 46 patients who had ileal pouches.

Forty-eight percent of patients were given a diagnosis of pouchitis based on a PDAI score of ≥7. No correlation was found between the symptom, endoscopy, and histology scores. Patients who had low clinical scores, but a PDAI of ≥ 7 decreased their PDAI by ≥ 3 points after 2 weeks of antibiotic therapy. The mean reductions in the total PDAI score, symptom, endoscopy, and histology scores were all significantly lower than before treatment. Conversely, 25% of patients who had clinical symptoms of pouchitis who did not meet the PDAI criteria for pouchitis did not respond symptomatically to empiric antibiotic therapy in the past. This latter group of patients can be classified as having irritable pouch syndrome.[11]

On endoscopy, the neoterminal ileum above the pouch should be normal; inflammation and ulceration here indicates Crohn's disease. Inflammation of the pouch mucosa with granularity, edema, mucosal hemorrhage, contact bleeding, and superficial ulcers can be present with varying degrees of severity.[12] Inflammation can be uniform throughout the pouch or more severe in the distal pouch.[13] Histopathologic findings in pouchitis include acute and chronic inflammatory cell infiltration, ulceration, and villous atrophy with crypt abscesses and hyperplasia.[14]

If pouchitis is refractory to medical therapy or has atypical components, further diagnostic tests should be performed to exclude alternate diagnoses. Infectious etiologies should be ruled out by stool sampling and pouch biopsy. Multiple cases in the literature document cytomegalovirus of the pouch in patients who had refractory pouchitis. Treatment with ganciclovir led to resolution of symptoms.[15,16]

Pouchography (luminal contrast study) can show ileoanal anastomotic separations, pouch fistulas, and anastomotic strictures. If Crohn's disease is suspected, a small bowel follow-through x-ray will rule out disease above the pouch. A computerized axial tomography (CAT) of the pelvis or magnetic resonance imaging will detect peripouch abscesses or inflammatory phlegmons. Endoluminal transpouch ultrasonography has also been used in pouch dysfunction with reported higher rates of fistula and abscess detection than both CAT scan and pouchography.[17] Anorectal manometry assesses for pelvic floor dysfunction and is another useful tool in evaluating poor pouch function. Finally, scintigraphic pelvic pouch emptying scans can be used to evaluate patients who have inefficient or inadequate pouch evacuation.[18] If a diagnosis of pouchitis is not made on endoscopic and histologic criteria and other disease states are ruled out, it is possible that the patient may have irritable pouch syndrome.[11] In these clinically symptomatic patients, treatment strategies similar to those used in irritable bowel syndrome (antidiarrheals, anticholinergics, antidepressants) may be used with some benefit.

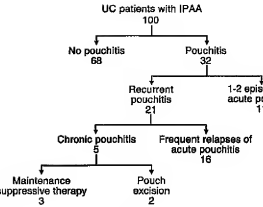

Figure 1. The clinical outcome of 100 patients at the Mayo Clinic who underwent ileal pouch anal anastomosis for ulcerative colitis. Reprinted with permission from Sandborn WJ. Pouchitis: Definition, risk factors, frequency, natural history, classification, and public health perspective. In: McLeod RS, Martin F, Sutherland LR, et al., eds. Trends in inflammatory bowel disease 1996. Lancaster, UK: Kluwer Academic, 1997:51–63.

Epidemiology, Risk Factors, and Natural History

Frequency

The cumulative risk of having one or more episodes of pouchitis varies from 15% to 53% in patients who have UC.[19–26] This wide range reflects the varied methods of defining and diagnosing pouchitis in the different studies. The rate of occurrence of a new diagnosis of pouchitis appears to be highest in the first 6 months after closure of the loop ileostomy, and then decreases significantly after 12 months.[24] The overall frequency of pouchitis is much lower in patients with FAP (3%–14%).[19,21,27] The frequency of refractory pouchitis ranges from 4.5% to 5.5%, with severe intractable pouchitis leading to excision of the pouch in 0.3% to 1.3% of patients. Figure 1 shows the clinical outcome of 100 UC patients at the Mayo Clinic who underwent IPAA.[9]

Predictive Factors

Pouchitis does not appear to have a predilection for age or race, although one small study did note a decreased incidence in African Americans when compared with Caucasians.[28] Males may have higher rates of chronic pouchitis.[29] Surgical technique does not seem to affect the frequency of pouchitis, although indication for

surgery (FAP vs. UC) does. Pouchitis rates are similar in J vs. K reservoirs,[30] S vs. W reservoirs,[31] one- vs. two-stage restorative proctocolectomy,[32] and in laparoscopic IPAA.[33]

Penna et al. found a cumulative risk of pouchitis in UC patients to be 15.5%, 22.5%, 36%, and 45.5% at 1, 2, 5, and 10 years after IPAA, respectively. This risk was much higher in patients who had primary sclerosing cholangitis (PSC), whose risk at 1, 2, 5, and 10 years was 22%, 43%, 61%, and 79%, respectively.[23] Stahlberg et al. found similar results with a cumulative risk of 51% at 4 years. All 6 patients (100%) who had PSC developed pouchitis, and extraintestinal manifestations (EIM) as a whole were a predictive factor for pouchitis.[24]

Many other studies report an increased frequency of pouchitis in patients who have EIM.[28,34–36] Seronegative arthritis responsive to steroids and associated only with active pouchitis has been reported.[37] Lohmuller et al. studied 734 patients who underwent IPAA. Patients with preoperative EIMs had a 39% incidence of pouchitis vs. 26% in those who did not. Patients who developed EIM after colectomy with IPAA had a 53% frequency of pouchitis vs. 25% in those who did not. Similar to UC, smoking may be protective against the development of pouchitis. Merrett reported a 33% frequency of pouchitis in former smokers, 25% in patients who never smoked, and 6% in current smokers.[38] These findings have been confirmed by other investigators.[24,28]

The importance of the extent of preoperative UC as a risk factor for the development of pouchitis is more controversial. Samarasekera found no relationship between distal colitis or more extensive disease and the frequency of pouchitis in 177 patients.[39] In contrast, Schmidt reported that colonic extent of disease had a significant association with the subsequent development of pouchitis after IPAA. However, the severity of the UC preoperatively was not found to be predictive.[40]

Backwash ileitis or inflammation in the terminal ileum as a risk factor for pouchitis is also controversial. One study found no correlation with development of pouchitis,[41] whereas another study found that the eosinophils and villous blunting in the terminal ileum were predictive of the degree of pouch inflammation.[40] The potential role of eosinophils is further supported by the finding of a 3-fold increase in the eosinophil concentration in preoperative colonic mucosa in patients who subsequently developed pouchitis versus those who did not.[42]

A genetic marker shown to predict the development of pouchitis is the interleukin-1 receptor antagonist gene (IL-1ra) allele 2. IL-1 is a major proinflammatory cytokine. IL-1ra competitively binds to IL-1 receptors without inducing signal transduction. However, IL-1ra allele 2 is associated with decreased levels of IL-1ra,[43] leading to an imbalance of IL-1ra/IL-1 which has been implicated in the pathogenesis of UC.[44] In a study by Carter,[45] patients who had pouchitis were found to have higher allele 2 carriage versus patients without pouchitis (72% vs. 45%). IL-1ra is not only a possible marker predicting pouchitis, but also a potential target for biologic therapy.

The predictive value of serum antineutrophil cytoplasmic antibody-perinuclear staining pattern (pANCA) is more controversial. The prevalence of pANCA in UC patients is 60%.[46] Whether this number is decreased after procrocolectomy[47,48] or unchanged[49–52] is uncertain. The literature is also divided as to whether there is a correlation between pANCA and the development of pouchitis. Four studies have found that the prevalence of pANCA is higher than expected in IPAA patients who have pouchitis (89% to 100%) and lower than expected in patients who do not have pouchitis (18% to 74%).[46,50,51,53] However, 7 more recent studies have shown that there is no correlation between pANCA and the occurrence of pouchitis.[34,48,52,54–57] Whether the failure of these later studies to show an association is based on the definitions of pouchitis used, the ANCA assay methodology, disease heterogeneity, or a true absence of association remains to be determined.

A provocative but small study by Fleshner[58] measured the quantitative levels of pANCA before colectomy for UC and divided them into high level (>100 EU/mL), moderate (40 to 100 EU/mL), and low level (<40 EU/mL). Sixty of 95 patients were pANCA-positive before colectomy, of which 9 were high-level, 32 moderate, and 19 low-level. pANCA (+) and pANCA (−) patients did not differ in the overall frequency of pouchitis (acute or chronic), and pANCA levels were not predictive of acute pouchitis. However, pANCA levels were predictive of chronic pouchitis: the cumulative risk of developing chronic pouchitis was significantly higher in patients with high-level pANCA (56%) than in moderate (22%), low-level (16%), or pANCA (−) patients (20%).[58]

PANCA levels are also increased in patients who have PSC.[59] PSC, in turn, is a risk factor for pouchitis.[23,47,60] Patients who have PSC and who undergo IPAA have a 63% chance of developing pouchitis versus only 32% for those who do not have PSC. The cumulative risk of developing pouchitis in patients who have PSC is also higher at 1, 2, 5, and 10 years than that in patients who have UC and do not have PSC.[23] The increased incidence of pouchitis in patients who have PSC and other EIM suggests that there may be a particular genotype of UC

Table 3. Predictive Factors for the Development of Pouchitis

1. Male gender (chronic pouchitis)
2. Primary sclerosing cholangitis
3. Extraintestinal manifestations
4. Nonsmoker
5. Extent of colitis[a]
6. Backwash ileitis[a]
7. Preoperative quantitative pANCA level (chronic pouchitis)[a]
8. IL-1ra gene allele 2

[a]Denotes that the data is mixed.

that has a stronger predisposition to develop pouchitis. PANCA may or may not be a serological marker for that genotype. These correlations also support the theory that pouchitis may be either a recurrence of UC in the pouch or a third, new form of inflammable bowel disease (IBD). Table 3 summarizes the potential predictive factors for the development of pouchitis.

Quality of Life

Aside from pouchitis, outcome after IPAA is variable and is dependent on surgical expertise. Most studies report an average of six bowel movements a day and some fecal incontinence in approximately 50% of patients.[61,62] Despite these numbers, the health-related quality of life (QOL) after IPAA has consistently been comparable to normal populations and is better than in active UC.[63–66] However, poor functional status, increased number of bowel movements, and chronic pouchitis do decrease health-related QOL.[66] Improved QOL overall after surgery but a worse QOL with pouchitis[67] has been confirmed by use of the Cleveland Global Quality of Life score, a tool specifically developed to assess patients with a restorative proctocolectomy.[68] The IBD questionnaire,[69] a QOL tool validated in UC and Crohn's disease, appears to correlate with PDAI and is another tool that can be used to measure QOL in patients who have pouchitis.[70]

Complications

The effect of acute pouchitis on long-term functional results is not clear. Whereas one prospective study of 137 patients found that even one episode of acute pouchitis can result in poorer long-term functional results,[20] Keranen et al. found that only chronic pouchitis affects functional outcomes.[72] Chronic pouchitis is rarely a cause for pouch excision.[62,71] Women who have IPAA have significantly lower fertility rates than those who have UC,[72] and while pregnant have poorer QOL scores[67] with transient worsening of pouch function.[73] The contribution of pouchitis to this is unknown.

Metabolic sequelae after IPAA have been found to be associated with pouchitis and include decreased levels of albumin, calcium, total cholesterol, triglycerides, and vitamin E. Vitamin A, B_{12}, and D deficiency have also been found.[74] Osteopenia has been found using bone densitometry testing in patients who have villous atrophy of the ileal reservoir, a hallmark of pouchitis.[75]

Etiology

The etiology of pouchitis is unknown. Speculation has centered on the role of genetic susceptibility, fecal stasis, and/or bacterial overgrowth, an altered balance of luminal bacteria (dysbiosis), nutritional deficiencies, ischemic complications of surgery, a novel third form of IBD, a recurrence of UC in the pouch, or a missed diagnosis of Crohn's disease. The significantly higher occurrence of pouchitis in patients who have UC versus FAP suggests that the mechanism is not related to surgical changes common to both diseases (i.e., ischemia and fecal stasis). However, the efficacy of antibiotics and probiotics in treating pouchitis suggests that the latter mechanism may play a role. The ileal pouch undergoes adaptive changes once it is exposed to the fecal stream. Functionally, it changes from a primarily absorptive organ to an organ of storage. The histopathologic changes that follow reflect this transition. Ileal pouches acquire certain colonic characteristics such as goblet cells, villous atrophy, and crypt hyperplasia; however, complete colonic metaplasia does not seem to occur.[76,77] The UC host may be genetically more susceptible to having an inflammatory response to insults in their adapted pouch mucosa, much as they are thought to be susceptible to such insults in their now resected colon. Table 4 summarizes the potential etiologies of pouchitis.

Treatment

The treatment of pouchitis is predominantly empiric given the few controlled trials available. To date, there have been at least 9 published controlled trials on the treatment of pouchitis.[78–86] Antibiotics are the mainstay of acute and chronic treatment, but probiotics may play a role in the maintenance of remission in chronic pouchitis. Table 5 lists the treatment options currently available.

Antibiotics

Metronidazole and ciprofloxacin are the first-line therapy for pouchitis. Evidence that metronidazole is effective comes from an "N-of-1" randomized trial[78] and a randomized controlled crossover trial which showed a 73% response (defined as a decrease in stool frequency) in 13 patients with chronic pouchitis. The placebo response was 9%.[79] Hurst et al. found that 41 of 52 patients

Table 4. Potential Etiologies in the Development of Pouchitis

Cause	Supportive evidence	Negative evidence	Reference nos.
Altered immunoregulation	+/− pANCA IL-1ra gene allele 2 ↑ Lymphocyte densities ↑ Inflammatory cytokines Extraintestinal manifestations		45, 58, 135, 136
Crohn's disease	Ileal inflammation Fistulas	Disease in pouch only	92
Fecal stasis Bacterial overgrowth Dysbiosis	Antibiotics Probiotics	Same bacterial count w/ or w/o pouchitis	137–140
Fecal bile acids		Same total bile acid concentration in pouchitis vs. healthy	92, 140, 141
Short chain fatty acids		No correlation between SCFA, pouchitis, fecal bacterial concentrations	140
Ischemia	↓ Mucosal blood flow	Same surgery as FAP Allopurinol ineffective	83, 142

(79%) with acute pouchitis responded to a 7-day course of metronidazole at 250 mg orally 3 times a day with complete relief.[27] Two small series found metronidazole to have a response rate of 100% when given as a topical solution instilled at 75 to 150 mg daily[87] or 40 to 160 mg daily.[88]

Hurst reported that 11 of 52 patients did not respond to metronidazole. These patients were then given ciprofloxacin 500 mg twice a day, of whom 8 (73%) responded. Thus, the overall antibiotic response rate was 96%.[20] A randomized trial by Shen[93] compared 2 weeks of treatment with metronidazole 20 $mg \cdot kg^{-1} \cdot day^{-1}$ to ciprofloxacin 1000 mg/day in patients who had acute pouchitis. Both drugs significantly reduced the PDAI score, but ciprofloxacin had a greater reduction in overall PDAI score (6.9 ± 1.2 vs. 3.8 ± 1.7, $P = .002$), symptom score (2.4 ± 0.9 vs. 1.3 ± 0.9, $P = .03$), and endoscopic score (3.6 ± 1.3 vs. 1.9 ± 1.5, $P = .03$) vs. metronidazole. None of the patients who were administered ciprofloxacin experienced side effects whereas 33% of the patients who were administered metronidazole had adverse events. The side effect profile of metronidazole includes dysgeusia, dyspepsia, nausea, and peripheral neuropathy. For many practitioners, these undesirable sequelae of thetapy have made ciprofloxacin the drug of choice for pouchitis therapy. Other antibiotics used with anecdotal success include amoxicillin/clavulanic acid, eryrhromycin, and terracycline.[89]

In patients who have chronic recurrent or refractory pouchitis, antibiotic combination therapy may be effective. Gionchetti used rifaximin 1 g twice daily in combination with ciprofloxacin 500 mg twice daily for 15 days in 18 patients who had chronic treatment resistant pouchitis.[90] Six of 18 (33%) had complete remission defined as a PDAI of 0. Ten of 18 (55.6%) had clinical improvement with a decrease of 3 points on their PDAI score, for a total response rate of 88.8%. An open-label trial of metronidazole 400 to 500 mg twice daily, plus ciprofloxacin 500 mg twice daily for 28 days in patients who had recurrent or treatment refractory pouchitis noted an 82% remission rate. The median PDAI scores before and after therapy were 12 (range, 8 to 17 points) and 3 (range, 1 to 10 points), respectively.[70]

An initial episode of pouchitis should be treated with ciprofloxacin 500 mg twice daily or metronidazole 250 mg 3 times a day for 7 to 10 days. Response should be seen within 2 to 3 days. Responding patients who experience recurrent episodes and are able to tolerate the medication should be retreated with the same regimen. Some patients who have chronic pouchitis will require anywhere from 500 mg of ciprofloxacin or 250 mg of metronidazole every third day to 500 mg ciprofloxacin twice daily or 250 mg metronidazole 3 times daily to maintain their response. Others may develop resistance and require combination antibiotic therapy or a rotating schedule of 3 or more antibiotics. If antibiotics fail, other therapeutic options should be considered. Patients who have chronic pouchitis should be considered for probiotic therapy as described below (Figure 2).[91]

Mesalamine

Anecdotal reports suggest a benefit from topical mesalamine.[12,92,93] Miglioli et al. describe three patients who had pouchitis after IPAA for UC. They were administered mesalamine as a suppository or enema at 1.2

Table 5. Treatment Options

Class	Efficacy	Example
1. Antibiotics	+ Acute pouchitis + Chronic pouchitis	A. Metronidazole[a] B. Ciprofloxacin[a] C. Amoxicillin/clavulanic acid D. Erythromycin E. Tetracycline F. Rifaximin + ciprofloxacin G. Metronidazole + ciprofloxacin[a]
2. Probiotics	+ Prophylaxis + Maintenance	A. VSL #3[a] B. *E. coli* Nissle 1917
3. Mesalamine	+/−	A. Mesalamine enemas B. Sulfasalazine C. Oral mesalamine agents
4. Corticosteroids	+/−	A. Corticosteroid enemas B. Budesonide suppositories C. Budesonide enemas[a] D. Oral corticosteroids
5. Nutritional agents	+/−	A. SCFA enemas/ suppositories[a] B. Glutamine suppositories[b] C. Inulin[a]
6. Immune modifier agents/ biologics	+/−	A. Cyclosporine enemas B. Azathioprine/6-mercaptopurine C. Infliximab
7. Oxygen free radical inhibitor	− prophylaxis	A. Allopurinol[b]
8. Smoking/ nicotine	+	A. Smoking B. Transdermal nicotine (?)
9. Antidiarrheal/ antimicrobial	+/−	A. Bismuth subsalicylate B. Bismuth carbomer enemas[b]
10. Surgical options		A. Ileal pouch exclusion B. Ileal pouch excision

[a]Denotes positive randomized controlled trial.
[b]Denotes negative randomized controlled trial.

to 4 g daily. After 20 to 30 days, clinical and endoscopic improvement was noted with partial histological recovery.[94]

The bacteria required to split the azo-bond in sulfasalazine and release the mesalamine moiety is present in the reservoir of patients after IPAA,[95] suggesting that sulfasalazine is a rational treatment modality. Pentasa may also achieve some release of mesalamine into the ileal pouch. However, there are no randomized controlled trials of any oral mesalamine agents for the treatment of pouchitis.

Corticosteroids

When antibiotics fail, oral and topical corticosteroids have been tried with limited anecdotal success.[92,93] A small open trial of budesonide suppositories was conducted in 10 patients who had active pouchitis. After budesonide 1.5 mg per day for 4 weeks, all patients had clinical and endoscopic improvement or remission, but 6 (60%) relapsed within 8 weeks.[96] A randomized, placebo-controlled trial of 2-mg budesonide enemas versus metronidazole also showed efficacy.[84] Twenty-six patients who had acute pouchitis by PDAI score ≥ 7 were randomized to either budesonide enemas or oral metronidazole 500 mg twice daily for 6 weeks. Fifty-eight percent of budesonide patients and 50% of metronidazole patients improved. Fifty-seven percent of metronidazole patients had adverse events versus only 25% of budesonide patients. Oral-controlled release budesonide has not been reported for the treatment of pouchitis, but anecdotal experience suggests that it may be effective (W. J. Sandborn, unpublished data, December 2002).

Immunosuppressive Therapy

MacMillan reported a small retrospective series of 4 patients who had chronic pouchitis that were treated with azathioprine or 6-mercaptopurine.[97] Patients were able to discontinue steroids and maintain a sustained response for up to 3 years. Immunosuppressive therapy is not protective against the development of pouchitis in the posttransplant setting. Zins reported 7 patients who had IPAA who underwent orthotopic liver transplanta-

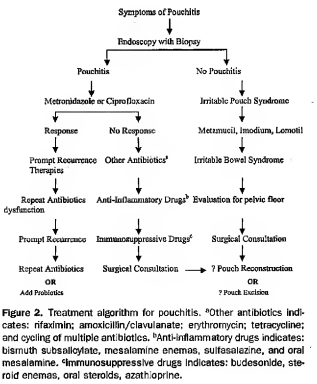

Figure 2. Treatment algorithm for pouchitis. [a]Other antibiotics indicates: rifaximin; amoxicillin/clavulanate; erythromycin; tetracycline; and cycling of multiple antibiotics. [b]Anti-inflammatory drugs indicates: bismuth subsalicylate, mesalamine enemas, sulfasalazine, and oral mesalamine. [c]Immunosuppressive drugs indicates: budesonide, steroid enemas, oral steroids, azathioprine.

tion for PSC.[98] Five of 7 had chronic or recurrent pouchitis before transplant, of whom 4 continued to have chronic pouchitis after transplant despite a triple immunosuppressive regimen of prednisone, azathioprine, and either cyclosporine or FK 506. One patient who had been free of pouchitis before transplant developed a single acute episode posttransplant. Similarly, Rowley reported that 1 of 4 patients with an orthotopic liver transplant for PSC who underwent colectomy with IPAA for UC developed chronic pouchitis despite immunosuppression with cyclosporine.[99]

Infliximab has been reported to be of benefit for treating Crohn's disease in the ileal pouch.[100] More recently, Arnott[101] reported that 2 patients who had refractory pouchitis responded to a single infusion of infliximab (response defined as a decrease in the number of bowel movements and less urgency) with benefit sustained to 12 weeks. No long-term follow-up information was provided.

Bismuth

Bismuth-containing carbomer foam enemas showed promising results in an open label trial.[102] Twelve patients who had treatment refractory chronic pouchitis were treated with 230 mg elemental bismuth-containing carbomer foam enemas. The enemas were given nightly for 45 days. Ten of 12 (83%) patients had a clinical response with a decrease in their PDAI scores by 2 points or more. Of these 10, 6 (60%) maintained their response over 12 months while receiving an enema every third night. No side effects were reported. Unfortunately, a randomized double-blind placebo control trial in 40 patients did not show a difference between placebo and bismuth carbomer foam enema in the treatment of chronic pouchitis.[81] Twenty patients received a placebo enema containing a gum resin and 20 patients received 270 mg of elemental bismuth complexed with carbomer delivered as foam enemas for 3 weeks. No patients achieved remission (PDAI of 0) but 9 patients (45%) in each group achieved a clinical response with a 3-point decrease in their PDAI. The investigators cite low concentrations of bismuth in the enemas, short duration of treatment, therapeutic efficacy of gum resin (given the high placebo rate of 45%), or a true treatment failure to explain the lack of efficacy of bismuth.

A retrospective series of 13 patients who had chronic pouchitis studied the effect of oral bismuth subsalicylate tablets (Pepto-Bismol, Proctor and Gamble, Cincinati, OH) on disease course. All patients were receiving antibiotics (metronidazole or ciprofloxacin) but remained symptomatic. All patients received an initial dose of eight 262-mg chewable bismuth subsalicylate tablets per day for 4 weeks. Eleven of 13 had a clinical response with a decrease in stool frequency, fecal inconrinence, and/or abdominal cramping. One patient reduced their dose secondary to bloating, while the 7 others reduced their dose because of similar benefit at the lower dose. Five of 11 responders were able to discontinue antibiotic use after 4 weeks.[103] These inconsistent results with bismuth indicate that an additional controlled trial of oral bismuth may be warranted.

Allopurinol

Allopurinol is a xanthine oxidase inhibitor. The theoretical basis for its use in pouchitis is to inhibit the production of free radicals and thus inhibit mucosal injury. A small trial by Levin et al. showed a 50% response rate in acute and chronic pouchitis.[104] Eight patients who had acute pouchitis received 300 mg twice daily of allopurinol. Four had resolution of symptoms. Fourteen patients who had chronic pouchitis were treated with the same dose for 28 days; 7 of 14 had a clinical response. However, a randomized controlled trial of allopurinol for the prophylaxis of pouchitis was negative.[83] In this study, 184 patients who had UC who were undergoing IPAA were randomized to receive postoperative allopurinol 100 mg twice daily or placebo. The cumulative risk of pouchitis was 31% in the allopurinol group and 28% in the placebo group, which was not significant. Additionally, there was no difference in overall pouch function between these 2 groups. These findings do not lend credence to the theory of ischemic damage and free radical injury contributing to the pathogenesis of pouchitis.

Nutritional Agents

Fiber. Thirlby et al. showed that oral fiber supplementation with either pectin, a soluble fermentable fiber supplement, or Citrucel (Glaxo Smith Kline, Research Triangle Park, NC), a methyl cellulose-based, nonfermentable fiber, has no benefit on stool frequency, pouch function, bloating, and stool consistency in patients after IPAA.[105] Inulin, a dietary fiber that is fermented to short-chain fatty acids (SCFA), was studied in a randomized placebo-controlled trial of 3 weeks duration.[86] Pouch patients receiving 24 g/day of inulin had increased butyrate concentrations (18.9 vs. 11.7, $P = 0.01$), decreased fecal pH (5.33 vs. 5.62, $P = 0.02$), decreased concentrations of *Bacteroides fragilis* (6.77 vs. 7.68, $P = 0.02$), and lower levels of some secondary bile acids in the feces compared with patients on placebo. The overall PDAI score was lower in inulin-treated patients (4.05 vs. 5.39, $P = 0.01$) than in placebo, with significantly lower endoscopic (0.95 vs. 1.47, $P = 0.04$) and

histologic scores (2.11 vs. 2.61, $P = 0.04$), but no difference in the clinical score (1.00 vs. 1.26, $P = 0.17$). However, because all of these patients did not meet the definition of pouchitis by PDAI score and there was no significant improvement in clinical symptom scores, the actual benefit to the patient of receiving inulin therapy is unclear.

Short chain fatty acids/glutamine. SCFA (acetate, propionate, butyrate) are produced by anaerobic bacterial fermentation. They are the major source of energy for the colonic mucosa.[106] Glutamine is the analogous energy source for the small intestinal mucosa. Studies reporting the use of SCFA as a treatment for pouchitis are limited, and the results are mostly negative. Two small series used the same SCFA enema formulation of 60 mmol/L sodium acetate, 30 mmol/L sodium propionate, and 40 mmol/L sodium *n*-butyrate in a combined total of 10 patients who had chronic pouchitis.[107,108] Only 3 patients had a clinical response whereas 2 patients actually had worsening of their clinical symptoms. Den Hoed described a single patient who had refractory pouchitis who completely responded to treatment with a similar SCFA enema.[109] Another study randomized patients with chronic pouchitis to either butyrate or glutamine suppositories for 10 days. Three of nine (33%) patients whose symptoms were treated with butyrate and 6 of 10 (60%) patients whose symptoms were treated with glutamine responded.[82] Given the lack of a placebo control, it is unclear whether these two therapies are similarly effective or similarly ineffective.

Smoking/Nicotine

Current smoking has been reported to be protective against pouchitis.[24,28,38] To date, there have been no trials of nicotine enemas or transdermal nicotine patch for the treatment of pouchitis.

Probiotics

Probiotics are live organisms, typically bacteria, found as commensals in the human gastrointestinal tract. Based on the hypothesis that an imbalance in the usual fecal flora (dysbiosis) may result in inflammatory conditions such as pouchitis, Gionchetti conducted a randomized double-blind placebo controlled trial of the probiotic formulation VSL-3 (Sitia-Yomo, Milano, Italy).[110] Forty patients who had chronic pouchitis in remission after treatment with antibiotics (PDAI = 0) received either placebo or a 6 g daily oral dose of VSL-3 for 9 months. VSL-3 contains 5×10^{11}/g of viable lyophilized bacteria consisting of 4 strains of lactobacilli (*L. acidophilus, L. delbrueckii* subsp. *bulgaricus, L. plantarum, L. casei*), three strains of bifidobacteria (*B. infantis, B. longum, B. breve*) and one strain of *Streptococcus salivarius* subsp. *thermophilus*. Seventeen of 20 patients (85%) who were treated with VSL-3 maintained remission (relapse was defined as an increase in the PDAI $\geq$ 2 points) compared to none of 20 patients who were treated with placebo. No adverse events were reported. The VSL-3–treated group was found to have an increase in fecal concentrations of lactobacilli, bifidobacteria, and *S. thermophilus* by day 15. A second controlled trial of VSL-3 for the treatment of chronic pouchitis was conducted in 36 patients with similar results.[111] VSL-3 is also more effective than placebo as a prophylaxis against the development of pouchitis in the first year after surgery.[112] A case report of 2 patients suggested that another probiotic, *Escherichia coli* strain Nissle 1917, may be of benefit for the treatment of active pouchitis and the maintenance of remission as well.[113]

The mechanism of action of probiotics in pouchitis is unclear. Patients who have pouchitis and who received probiotic therapy with VSL-3 were found to have increased concentrations of the anti-inflammatory cytokine IL-10 and a reduction of the proinflammatory cytokines IL-1α, interferon-γ, and tumor necrosis factor-α, as well as inducible nitric oxide synthase and matrix metalloproteinase activity to concentrations similar to those found in noninflamed pouches.[114] *E. coli* Nissle 1917 was able to induce IL-8 while VSL-3 was not, suggesting that these 2 probiotic formulations may have different modes of action.[115]

Crohn's Disease

When Crohn's disease is diagnosed in the pouch (based on pre-pouch ileitis or fistula involving the pouch), treatment is similar to the treatment of Crohn's disease elsewhere in the gastrointestinal tract. Berrebi reported on 2 patients who had IPAA and were diagnosed with Crohn's disease in the reservoir. Both responded to corticosteroid and azathioprine therapy, with eventual maintenance on azathioprine alone.[116] Ricart reported a series of 7 patients who had IPAA for UC who were subsequently diagnosed with Crohn's disease and who were refractory to conventional therapy. These patients were treated with infliximab. Six patients had a complete response with closure of all fistulous tracts, and one had a partial response.[100]

Pouch Excision

Pouch excision is rare and occurs more commonly for pouch dysfunction than for true chronic pouchitis. However, Penna et al. estimate that approximately 1.3% of patients who undergo IPAA for UC will need a pouch excision for chronic treatment refractory pouchitis.[23]

Dysplasia

There have been at least 17 cases of adenocarcinoma arising in the permanent (Brooke) ileostomy of patients who had UC. The case described by Reissman notes diffuse colonic metaplasia in the ileostomy around the adenocarcinoma with sulfomucin production.[117] In 1997, the first case of an adenocarcinoma arising in a continent ileostomy (Kock pouch) was described in a patient who had UC. The pouch mucosa showed chronic inflammation with villous atrophy and mild to moderate dysplasia.[118] It was not clear if this patient suffered from recurrent pouchitis. Also in 1997, a case of large cell lymphoma arising in the pouch of a patient who had had UC was described. This patient suffered from chronic refractory pouchitis, which may in retrospect have been due to the invasive lymphoma, undetected until surgical resection of the pouch for pouch dysfunction.[119]

Rectal cancer has developed after IPAA in the residual columnar epithelium or rectal cuff.[120–122] Although this makes intuitive sense, the risk of dysplasia and adenocarcinoma developing in the ileal reservoir has been mostly a theoretical concern. However, dysplasia has now been noted by 3 groups in the ileal reservoir including the development of adenocarcinoma of the pouch in one patient who had chronic pouchitis.[123–126]

In 1991, Lofberg et al.[127] reported the first case of pelvic pouch dysplasia. The patient was a 36-year-old man who underwent a colectomy, mucosal proctectomy, and IPAA with a S-type pelvic pouch. No dysplasia was noted in the colectomy specimen. The patient suffered from chronic pouchitis and was on long-term metronidazole therapy. Four years after pouch creation, he was noted to have low-grade dysplasia on biopsy and DNA aneuploidy by flow cytometry. The patient then underwent periodic surveillance pouchoscopy with biopsy, and in 1996 high-grade dysplasia was detected.[126] In 1997, the patient was diagnosed with primary cholangiocarcinoma, with likely underlying subclinical PSC.[128]

In 1995, the same group reported the results of 87 patients who had IPAA for UC whose cases were followed for a mean of 6.3 years. Three types of mucosal adaptation were noted in the reservoir. Type A (51% of patients) was characterized by normal mucosa or a mild villous atrophy and no or mild inflammation. Type B (40% of patients) showed transient atrophy with temporary moderate or severe villous atrophy followed by normalization. Finally, Type C (9%) showed constant atrophy with permanent total or subtotal villous atrophy accompanied by severe pouchitis. It was in this last group that low-grade dysplasia was found in 3 of 8 patients. This group also had the highest level of sulfomucin-producing goblet cells in the pouch.[124] A prospective follow-up study of 7 patients who had Type C mucosa and 14 who had Type A patterns was performed. Dysplasia was noted in 5 of 7 Type C pouches (71%) (4 low-grade dysplasia and 1 high-grade dysplasia). There was no correlation with dysplasia in the colectomy specimen, but there was an association with an early onset of UC. The investigators believed that patients who were identified as having a Type C response 4 years after ileostomy closure should have at least annual pouchoscopy with surveillance for dysplasia.[126]

Other investigators have not found dysplasia on surveillance of the pouch,[129–132] but have found similar rates of Type A, B, and C mucosa in adults[131] and children[132] who have an IPAA for UC. Setti Carraro confirmed the finding that only patients who had Type C mucosa developed chronic pouchitis. He also noted that the categorization of response type could be made at 6 months after ileostomy closure.[131] In a study of six patients who had chronic severe pouchitis, one had a genetic alteration associated with colorectal carcinoma, a loss of heterozygosity at 5q15-22.[133]

In 2001, Thompson-Fawcett[123] surveyed the pelvic pouches of 106 patients who had potential risk factors for dysplasia—chronic pouchitis, pelvic pouch for 12 years or more, Kock pouch for 14 years or more, and neoplasia in the colectomy specimen. One patient who had a long-standing pouch had multifocal low-grade dysplasia. She had never had an episode of pouchitis and opted for pouch excision.

In 2000, Iwama reported a case of adenocarcinoma in a J-pouch that had been outside of the fecal stream for 18 years.[134] In 2001, Heuschen et al. reported the first adenocarcinoma of a functioning pelvic pouch that clearly developed from the ileal mucosa.[125] This was a patient who had pancolitis and backwash ileitis who underwent IPAA for multifocal dysplasia. The patient developed chronic pouchitis and was noted to have a tubulovillous neoplasia on pouch biopsy 3 years after surgery. Pouch excision was performed and a flat carcinoma in the proximal pouch was found.

Overall, pouch dysplasia is very rare. No screening program is currently advocated for patients with IPAA after colectomy for UC. Further studies are needed to delineate which patients need screening, when, where within the pouch, and how often. Potential risk factors for pouch dysplasia may be dysplasia in the original colectomy specimen, chronic pouchitis, and the age of the pouch. It is reasonable, based on the available data, to perform random mucosal sampling in the reservoir of all

patients who have a history of UC and a pouch 1 year after closure of the ileostomy. Those found to have Type C mucosal changes and/or chronic pouchitis should undergo annual surveillance pouchoscopy, as is done for patients who have UC. Patients who have dysplasia on colectomy may need to be surveyed regardless of evidence for chronic pouchitis.

Summary

Pouchitis is an idiopathic inflammatory disease of the ileal reservoir in patients who have undergone IPAA. Approximately half of all UC patients who undergo this procedure will have at least 1 episode of pouchitis with approximately 15% experiencing a chronic course. PSC and other BIM increase the likelihood of developing pouchitis, whereas smoking is protective. Similar genetic and autoimmune mechanisms to UC appear to occur in an ileal reservoir that shows increasingly colon-like adaptations with respect to bacterial content and mucosal characteristics. Although most patients have a good response to antibiotic therapy, increasing evidence supports a role for probiotics in prevention and maintenance. Finally, dysplasia is a rare but real concern, and pouch surveillance guidelines must be developed.

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Received January 6, 2003. Accepted February 20, 2003.

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